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ORBITAL IMPLANT OF MOURA BRAZIL

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Johannesburg

The last 10 years have witnessed a great effort on the part of ophthalmologists to improve the cosmetic appearance of the patient who has lost an eye. Until the advent of methyl methacrylate and other improved acrylic materials later introduced, the responsibility of the surgeon ceased with the removal of the offending organ.

When simple enucleation is performed certain deformities ensue. There is retraction of the socket caused by loss of the volume of the eye and contraction of the muscles. A deep orbito-palpebral sulcus appears on the upper lid, and there is a sagging of the lower lid. Movement is very limited. The mechanism by which these changes are brought about has been shown by Culler, who constructed a working model of the orbit. There is now no doubt that some form of implant should be used to prevent these complications.

A large variety of implants are available. They fall into 2 main classes, the completely buried type and the integrated or semi-buried type. The buried implants are usually well tolerated and are retained indefinitely but do not give perfect motion to the prosthesis since they are separated from it by Tenon's capsule and the conjunctiva. The semi-buried variety, while imparting excellent lifelike mobility, are liable to become infected, and if this complication develops they are likely to become extruded.

Cutler has set certain criteria by which to judge the results of all procedures:

1. Elimination of the deep sulcus of the upper lid.
2. Prevention of sagging of the lower lid.
3. 'Lifelike' movement.
4. Reduction of excessive secretion and infection.
5. Permanence of the fixation and retention of the implant.

An implant of the semi-buried variety which fulfils all the criteria was perfected by a Brazilian colleague, Moura Brazil do Amaral. He noted that if the pegs of an implant were buried some distance from the conjunctival wound they would slowly extrude through Tenon's capsule and conjunctiva, which remain perfectly healthy. This technique was first outlined at the Havana Congress in 1948. The implant itself is acrylic, about 16 mm. in diameter and perforated by 4 tunnels for the rectus muscles. Two pegs made of 22-carat gold, about 7 mm. long, are attached to its anterior surface. The motion transmitted by the ocular muscles *via* the pegs to the prosthesis quite often approaches normal.

Scrupulous attention to detail must always be observed during the operation to prevent complications and ensure that the implant is correctly positioned without undue tension on the enveloping structures. The implant itself should have been immersed for several hours in an aqueous antiseptic solution. General anaesthesia is preferred, but the operation can be performed under local anaesthesia with the use of a retrobulbar and intramuscular injection of anaesthetic solution. Adequate premedication should be given.

The Technique: After the lids have been adequately separated by means of a suitable speculum the conjunctiva is incised at the limbus around the circumference of the cornea. It is important to preserve as much conjunctiva as possible, because good mobility is impossible in a contracted, tense socket. The conjunctiva and Tenon's capsule

Fig. 1. Photograph showing pins. Note the cleanness of the socket.

are then dissected as far as the insertions of the tendons of the rectus muscles. Johnson advocates removal of the tendons with a strip of sclera attached, because this makes identification of the tendons easier, increases the mobility of the implant and aids in the suturing of the tendons over the implant. Care must be taken not to injure the levator when the superior rectus tendon is severed. Next the superior oblique and the inferior oblique tendons are severed from the globe. The globe is then proptosed by partially closing the speculum and pushing it behind the eyeball. At this stage the optic nerve is severed by means of a wire snare or scissors. Proper haemostasis is rapidly obtained by means of haemostatic sponges. Only after all bleeding has stopped is the implant inserted. Then the horizontal recti are passed through their tunnels and sutured to each other. Next the vertical recti, after being passed through their tunnels, are sutured to each other and then to the horizontal recti. The edges of Tenon's capsule are then sutured with 5-0 catgut so as to bury the implant and pegs. Finally the conjunctival wound is carefully closed with interrupted sutures, antibiotic ointment is applied to the conjunctival sac, and a pressure bandage is applied.

The pegs usually become extruded within 2 weeks, but if they do not, then they should be assisted. Moura Brazil has designed an instrument resembling a comedone expressor to assist the freeing of the pegs. After some weeks the prosthesis can be fitted.

The outstanding features of this type of implant are the rapid, synchronous movements and the absence of secretion. The patients are delighted with the result. One patient, a circus actor who had an implant operation performed by Dr. Moura Brazil about 7 years ago, allows members of the audience to poke him in the 'eye' as part of his act.

Complications: The conjunctival wound may partially open a few weeks after surgery, but it usually closes again without interference. A more serious complication is thinning of the conjunctiva over the implant, although this rarely leads to extrusion. It is unsatisfactory to suture the tear, for the conjunctiva is very thin at the margins. Jaffe employs a technique which utilizes the thick conjunctiva of the fornices. Horizontal incisions are made in the upper and lower fornices, extending from the medial margin to the lateral margin of the fornix. The incisions need only be deep enough to allow the conjunctiva to be drawn over the tear. The thin margins of the tears are excised, and the wounds in the upper and lower fornices are sutured. A conformer should be used for several days.

SUMMARY

An orbital implant is described which appears to be well tolerated and free of the usual complications of the semi-buried variety.

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CHARGES FOR ANTI-POLIOMYELITIS IMMUNIZATION

The Northern Association of Medical Aid Societies has asked the *Journal* to publish for the information of members of the Association the following list of medical aid societies within the Association, grouped according to the way they deal with charges in respect of anti-poliomyelitis immunization:

A. *Medical Aid Societies which do meet Charges*

The Argus Medical Benefit Society.
A.T.E. Medical Aid Society.
Building Societies Joint Medical Aid Fund.
Breyton Coalfields Benefit Society.
Corner House Insurance Fund.
Friend Medical Aid Fund.
Greatermans Medical Aid Society.
Hollerith Medical Aid Society.
I.W.S. Medical Aid Society.
K. & L. Timbers Ltd. Staff Medical Aid Fund.
Legal & General Medical Aid Scheme.
New Consolidated Gold Fields Employees' Medical Aid Fund.
The Northern Medical Aid Society.
Ore & Metal Medical Aid Society.
Pretoria Portland Cement Co. Ltd.
Reunert & Lenz Ltd. Medical Aid Society.
S.A. Mutual Fire & General Insurance Co. Ltd.
Traduna Medical Aid Fund.
United Building Society Medical Benefit Fund.
Architects' and Quantity Surveyors' Medical Aid Fund.

B. *Medical Aid Societies which do* not *meet Charges*

Anglo-Alpha (Roodepoort) Benefit Society.
African Explosives Medical Aid Society.
African Cables Medical Benefit Fund.
A.T.I. Medical Aid Society.
Bloemfontein Municipal Employees Medical Aid Society.
Chamber of Mines Medical Aid Society.
Germiston Industries Medical Aid Society.
Hubert Davies Johannesburg Staff Medical Aid Society.
The Johannesburg Board of Executors Medical Aid Society.
Sasol Medical Benefit Society.
S.A.A.M.E. Medical Aid Fund.
South African Torbanite (Boksburg) Medical Aid Society.
Safim Medical Aid Society.
The Yorkshire Medical Aid Society.
Standard Brass Medical Aid Society

C. *Medical Aid Societies which pay Visiting Fee only (Member charged for Material)*

African Oxygen & Acetylene (Pty.) Ltd. Medical Aid Society.
A.A. Mutual Insurance Association Limited.
Transvaal Society of Accountants Medical Aid Fund.
South African Press Association Medical Aid Society.
Hunt, Leuchars and Hepburn Ltd. Transvaal Staff Medical Aid Society.
University of the Witwatersrand (Johannesburg) Staff Medical Aid Fund.

D. *Medical Aid Society which pays for cost of Vaccine only*

Iscor Medical Benefit Fund.

E. *Medical Aid Society which pays two-thirds of Injection Fee only*

Rand Public Service Medical Aid Society.

F. *Medical Aid Society which pays the Doctor but recovers in full from the Member*

Everite Medical Aid Society.

South African Medical Journal

Suid-Afrikaanse Tydskrif vir Geneeskunde

EDITORIAL

ORAL TREATMENT OF DIABETES MELLITUS

D 860 (tolbutamide, Rastinon, Orinase, etc.) has replaced the more toxic BZ 55 (carbutamide) in the new oral therapy for diabetes. Trials of both these substances are reported by South African workers. In the present issue (page 142) an article is published by Schneider and Politzer, of Johannesburg, reporting a series of diabetes cases treated with BZ 55 and another series treated with D 860. The results of treatment with BZ 55 at Cape Town were published in articles by Jackson, Linder and their co-workers[2,3] which appeared in the *Journal* of 22 December 1956, and these are followed in the present issue (page 146) by reports on the use of D 860 by the same group of workers.

The findings both at Cape Town and Johannesburg in general confirm those of the German authors[1] and indicate the potential value of D 860 in the treatment of the 'mild' middle-aged or elderly diabetic, and its almost total lack of value in the younger, severe, ketosis-prone subjects. They do not, however, confirm the statements that have been made that the best indication for D 860 is the obese diabetic of recent origin. It is, in fact, pointed out that the obese patient should be treated primarily by weight reduction, which means a low-calorie diet, after which the diabetes usually ceases to be a problem. Hence, it is likely that the main value of D 860 will be in the mild, older, diabetic who is not obese; perhaps even more particularly in the over-thin patient, who may then be allowed a more liberal, and even completely free, diet. In a number of cases it has been found possible to replace insulin therapy by treatment with D 860 (or BZ 55), but reference is made to the danger of the sudden cessation of insulin in the more severe diabetic, who may lapse into a coma, for the prevention of which D 860 is completely useless. It is imperative therefore that care and expert supervision should be used during the change-over from insulin to D 860, and our authors are agreed that this substance should be sold to the public only on a doctor's prescription.

The German workers report on a few cases of 'secondary' diabetes treated with D 860. Of 3 cases of acromegaly, 2 failed to respond, while the one who did respond was

VAN DIE REDAKSIE

MONDELINGE BEHANDELING VAN DIABETES MELLITUS

D 860 (tolbutamied, Rastinon, Oranase, ens.) het die meer toksiese BZ 55 (karbutamied) by die nuwe mondelinge terapie vir suikersiekte vervang. In die huidige uitgawe (bladsy 142) word 'n artikel deur Schneider en Politzer, van Johannesburg, gepubliseer, waarin 'n reeks van suikersiekte-gevalle wat met BZ 55, en 'n ander reeks wat met D 860 behandel is, gerapporteer. Die resultate van behandeling met BZ 55 in Kaapstad is gepubliseer in artikels deur Jackson, Linder en hulle medewerkers[2,3] wat in die *Tydskrif* van 22 Desember 1956 verskyn het, en hierdie artikels word in die huidige uitgawe (bladsy 146) gevolg deur verslae oor die gebruik van D 860 deur dieselfde groep navorsers.

Die bevindinge beide in Kaapstad en Johannesburg bevestig oor die algemeen dié van die Duitse outeurs[1] en dui die potensiële waarde van D 860 aan by die behandeling van die middeljarige of bejaarde suikersiektelyer wat die siekte in 'n ligte graad het, en die byna algehele waardeloosheid daarvan by die jonger, strawwe, ketose-geneigde pasiënte. Hulle bevestig egter nie die bewering wat gemaak is dat die beste aanduiding vir D 860 by die vetsugtige pasiënt is, by wie die suikersiekte van onlangse oorsprong is, nie. Dit word inderdaad daarop gewys dat die vetsugtige pasiënt in die eerste plek met gewigsvermindering, wat 'n lae-kalorie dieet behels, behandel behoort te word, waarna die suikersiekte gewoonlik nie meer 'n probleem is nie. Dit is dus waarskynlik dat D 860 van die grootste nut by die ligte graad, ouer suikersiektelyer, wat nie vetsugtig is nie, sal wees; miskien selfs meer bepaald by die té maer pasiënt, wat dan toegelaat kan word om 'n meer liberale en selfs heeltemal vry, dieet te volg. By 'n aantal gevalle is dit moontlik gevind om insulien-terapie deur behandeling met D 860 (BZ 55) te vervang, maar daar word verwys na die gevaar van die skielike staking van insulien by die ernstiger suikersiektelyer wat in 'n koma mag sink, die voorkoming waarvoor D 860 geheel en al nutteloos is. Dit is dus noodsaaklik dat sorg en deskundige toesig uitgeoefen behoort te word wanneer daar van insulien na D 860 oorgegaan word, en ons outeurs is dit eens dat hierdie stof slegs aan die publiek op 'n dokter se voorskrif verskaf behoort te word.

Die Duitse navorsers meld 'n paar gevalle van ‚sekondêre' suikersiekte, wat met D 860 behandel is, aan. Van drie gevalle van akromegalie het 2 nie gereageer nie, terwyl die een wat wel gereageer het, slegs suikersiekte in 'n ligte

only mildly diabetic and previously treated with diet only. All patients with Cushing's syndrome and diabetes responded well although, strangely enough, D 860 was of no value in controlling the hyperglycaemia induced by cortisone therapy. One case of haemochromatosis was a D 860 failure. One patient with diabetes following partial pancreactectomy, who needed 20 units of insulin daily, was stabilized instead on 1 g. of D 860 per day. Jackson *et al.* have observed 4 patients with chronic pancreatitis; 3 with severe diabetes completely failed to respond even to large doses while one, in whom the diabetes was comparatively mild, responded reasonably well.

How the new drugs (D 860 and BZ 55) operate it is hard to say. One thing that appears certain is that they will not reduce blood sugar unless some insulin is already present. Furthermore they definitely act much more markedly with endogenous insulin (as in the mild elderly diabetic) than with injected insulin. It is considered by some that the clinical facts fit best with the theory that these new drugs have a direct stimulating effect on pancreatic beta-cells.

There are a few odd points concerning D 860 which are of practical value. First, owing to the absence of the amino group which is present in BZ 55, it cannot readily be measured in the circulating blood. Such estimations as have been made have actually necessitated the use of D 860 labelled with radio-active sulphur 35. Secondly its excretion product in urine is precipitated by acid and therefore gives a false positive test for albumen on the sulphosalicylic method. The boiling test will be necessary as a routine in patients on treatment. Thirdly its presence causes a distinct increase in the non-protein nitrogen in the blood. Blood-urea estimations, which depend on a specific enzyme, will not be affected. Fourthly, a few people apparently become intolerant to alcohol while on D 860. It may be necessary to warn patients of this possibility.

A comparison of D 860 with BZ 55 reveals the following differences. Probably D 860 is a little less powerful in its blood-sugar reducing capacity, although in occasional patients (2 in the Cape Town series) it proves more effective than BZ 55. Apparently D 860 has no ill effect whatsoever on the blood-forming cells, whereas BZ 55 sometimes causes severe agranulocytosis and thrombocytopenia. Further, D 860 has virtually no antibacterial effect (slight inhibition of gram-positive cocci only, as opposed to the sulphonamide effect of BZ 55). Finally the evidence of untoward symptoms and allergic reactions are very much less on D 860. Roughly 1% of patients treated develop a mild urticarial rash, as against some 9% on BZ 55.

We cannot foresee the final place of D 860 in diabetes, nor do we know anything of long-term therapy, but one thing is certain, that the demand for it will be enormous.

1. Symposium (1956): Dtsch. med. Wschr., **81,** 823 and 887.
2. Saunders, S. J. *et al.* (1956): S. Afr. Med. J., **30,** 1222.
3. Jackson, W. P. U. *et al.* (1956): *Ibid.*, **30,** 1227.

graad gehad het en voorheen net met dieet behandel is. Alle pasiënte met Cushing se sindroom en suikersiekte het goed gereageer alhoewel, vreemd genoeg, was D 860 waardeloos om hiperglisemie, wat deur kortisoon-terapie aangebring is, te beheer. Een geval van hemokromatose was 'n D 860-mislukking. Een pasiënt met suikersiekte, wat op gedeeltelike pankreatektomie gevolg het, en wat 20 eenhede insulien daagliks nodig gehad het, is in plaas daarvan op 1 g. D 860 daagliks gestabiliseer. Jackson *et al.* het 4 pasiënte met chroniese pankreatitis waargeneem; 3 met strawwe suikersiekte het geheel en al nie selfs op groter dosisse gereageer nie, terwyl een wat suikersiekte in 'n betreklike ligte graad gehad het, redelik goed gereageer het.

Dit is moeilik om te verklaar hoe die nuwe middels (D 860 en BZ 55) werk. Een feit waaromtrent daar sekerheid skyn te wees, is dat hulle nie bloedsuiker sal verlaag tensy daar nie alreeds 'n bietjie insulien aanwesig is nie. Boonop werk hulle bepaald meer opvallend met endogene insulien (soos by die ligte graad, bejaarde suikersiektelyer), as met ingespuite insulien. Dit word deur sommige beskou dat die kliniese feite beter inpas met die teorie dat hierdie nuwe middels 'n direkte stimulerende effek op pankreatiese betaselle het.

Wat D 860 aanbetref, is daar 'n paar vreemde eienskappe wat van praktiese waarde is. Eerstens, weens die afwesigheid van die aminogroep wat in BZ 55 aanwesig is, kan dit nie met gemak in die sirkulerende bloed gemeet word nie. By sodanige skattings wat gemaak is, was dit inderdaad nodig om D 860, wat met radio-aktiewe swael 35 gemerk was, te gebruik. Tweedens, sy uitskeidingsproduk in urien word verhaas deur suur en gee dus 'n valse positiewe toets vir eiwit met die sulfosalisiliese metode. Die kooktoets sal nodig wees as roetine by pasiënte wat behandel word. Derdens, sy aanwesigheid veroorsaak 'n duidelike vermeerdering van die nie-proteïen stikstof in die bloed. Skattings van bloed-ureum, wat van 'n spesifieke ensiem afhang, sal nie geaffekteer word nie. Vierdens, sommige mense, terwyl hulle met D 860 behandel word, kan oënskynlik nie alkohol verdra nie. Dit mag nodig wees om pasiënte teen hierdie moontlikheid te waarsku.

'n Vergelyking van D 860 met BZ 55 bring die volgende verskille aan die lig. Waarskynlik is D 860, sover dit sy kapasiteit vir bloedsuiker-vermindering aanbetref, 'n bietjie minder kragtig, alhoewel dit af en toe by pasiënte (2 in die Kaapstad-reeks) meer effektief as BZ 55 geblyk het. Oënskynlik het D 860 hoegenaamd geen nadelige uitwerking op die bloedvormende selle nie, terwyl BZ 55 somtyds strawwe agranulositose en trombositopenie veroorsaak. Verder, D 860 het feitlik geen antibakteriese uitwerking nie (slegs geringe onderdrukking van grampositiewe kokke, in teenstelling met die sulfonamiede uitwerking van BZ 55). Ten slotte, die bewyse van teenspoedige simptome en allergiese reaksies is baie minder met D 860. Naasteby 1% pasiënte wat behandel word, ontwikkel 'n ligte netelroosuitslag, in vergelyking met min of meer 9% op BZ 55.

Ons kan nie vooruitsien wat die finale plek van D 860 by suikersiekte gaan wees nie, en ons weet niks van lang-termyn terapie nie, maar een ding staan vas, naamlik, dat die aanvrag ontsaglik sal wees.

1. Simposium (1956): Dtsch. med. Wschr., **81,** 823 en 887.
2. Saunders, S. J. *et al.* (1956): S. Afr. T. Geneesk., **30,** 1222.
3. Jackson, W. P. U. *et al.* (1956): *Ibid.*, **30,** 1227.

PAPER TESTS FOR GLYCOSURIA

Recently a very simple method of testing urine for glucose has become available from commercial sources. A strip of filter paper is impregnated with highly purified glucose oxidase, o-tolidine, and a vegetable peroxidase. If this strip is dipped in urine containing glucose and then withdrawn, the tiny quantity of glucose absorbed onto the strip is oxidized in the presence of the atmospheric oxygen under the influence of the oxidase enzyme. Gluconic acid and hydrogen peroxide are produced, and the latter reacts with the o-tolidine to form a blue dye. The degree of blueness then roughly indicates the amount of glucose.

'Tes-tape'[1] and 'clinistix' are available for purchase. 'Tes-tape' contains a yellow dye in addition to the above-mentioned substances, so that a colour ranging from yellow (no sugar) through light and dark green to very dark blue can be produced according to the glucose concentration. A colour scale provided with the tape purports to indicate colours corresponding to 0, 0·1, 0·25, 0·5 and 2% of glucose in the urine.

The great potential value of such a simple method plainly requires careful evaluation of its accuracy and of the place it should play in the detection and management of the diabetic. Two recent articles[2,3] in the *British Medical Journal* describe results of such evaluation and are of very great value, especially since unpublished observations in this country are in general agreement with them.

First, as regards specificity, the new method is a distinct advance on copper-sulphate reduction techniques (e.g. Fehling's and Benedict's tests), which do not differentiate between one reducing agent and another. Now the tapes owe their effect to an enzyme which is specific for glucose only, so that they can even distinguish glucose from other reducing sugars such as lactose. Plainly, therefore, they will be of particular value in testing urines from patients during late pregnancy and lactation, in whom Benedict's reagent may yield false positive results caused by lactose. Formerly the differentiation necessitated rather delicate chemical techniques (such as osazone formation), paper chromatography or the fermentation reaction. There is a snag, however, in this absolute specificity. The rare cases of galactosuria and pentosuria would be missed, and consequently it may be better to continue the use of the Benedict reagent in the urine testing of children.

Secondly as regards sensitivity, the paper compared well with the older methods and will detect quite small quantities of urinary glucose. The limit of sensitivity is, as claimed by the manufacturers, about 0·1 g. per 100 ml. This property, combined with the specificity, makes the papers particularly suited to the certain detection of small amounts of glucose in urines during routine testing, as in an out-patient department or doctor's surgery, and thus rescues us from the very many annoying doubtful 'green' tests found with the Benedict method.

It is as regards quantitative accuracy that the tapes fall down. Both groups of authors[2,3] agree that the reasonable accuracy required is not attained. The colour changes are not sufficiently plain to enable one to distinguish between 0·5% sugar and 2 or 5%, while in some instances even lesser amounts than 0·5% gave a very deep blue colour. Now the established diabetic is not so interested in accurate detection of tiny amounts of glucose, but the approximate degree of glycosuria is what he wants to know. This is just what the new tests will often fail to tell him. Consequently the paper method cannot be recommended for use in the control of diabetes and for routine use by severe diabetics, though it may be of value in mild cases, who usually and easily keep their urine free of sugar.

In summary, therefore, 'tes-tape' is likely to be of particular value in doctor's surgeries, and hospital out-patients and casualty departments, and of value in routine urine-testing in wards, in the control of the mild diabetic, and particularly in the obstetric department. It will be of little value in medical or other wards where diabetics are being controlled, nor will it be of sufficient accuracy for home use by the diabetics themselves.

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2. Hunt, J. A., Gray, C. H. and Thorogood, D. E. (1956): Brit. Med. J., **2**, 586.
3. Tunbridge, R. E., Paley, R. G. and Coulson, D. (1956): *Ibid.*, **2**, 588.

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BZ 55 AND D 860 IN THE TREATMENT OF DIABETES MELLITUS

T. SCHNEIDER AND W. M. POLITZER

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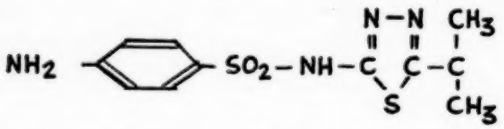
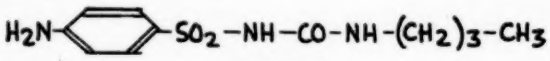
The search for an oral substitute for insulin has been in progress for a considerable time. It was first Watanabe[1] who found that guanidine decreased the blood sugar in rabbits; this, however, was not due to insulin action but to toxic effects on the liver. Evidence was presented by Vonkennel and Kimmig[2] in 1941 and confirmed by Janbon[3,4] in 1942 that sulphonamides lowered the blood-sugar level. These findings provided the stimulus for further work and in 1955 two chemically and pharmacologically similar compounds which had a lowering effect on the blood-sugar level were discovered.[5,6] The experimental names given to these preparations were BZ 55 and D 860.

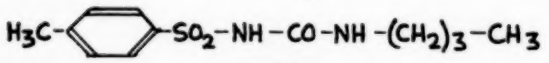
The formula of the original preparation used by Vonkennel and Kimmig[2] (p-aminobenzene-sulphamido-isopropyl-thiodiazole = IPTD) was:



The formulae of BZ 55 and D 860 are as follows:



BZ 55



D 860

It will be noted that these two compounds differ in that in D 860 a methyl group takes the place of an amino group in BZ 55.[7,8,9]

Effects

Both these preparations are absorbed very rapidly from the bowel and have been found to decrease the blood sugar, both in animals[5] and in humans.[3,6]

A lowering of the blood sugar by 30% has been noted in animals up to 72 hours after a single dose. In humans the hypoglycaemic effect has been found to occur particularly in the older age-group and in those in whom the diabetes is of recent origin.[6,10-12] Mohnike and Ulrich[13] found that in patients who had been satisfactorily controlled on D 860 hyperglycaemia only returned between 5 days and several weeks after discontinuing the preparation.

Side-effects. Serious hypoglycaemia has not been reported in the use of either drug (BZ 55 or D 860) except when they have been used in conjunction with insulin.[14]

Side-effects of BZ 55 so far noted have been those common to the sulphonamide group as follows: (*a*) Sensitization reactions, viz. fever and rash;[6,15] Bertram *et al*,[6] have noted these effects in 7·3% of their cases. (*b*) Blood changes, viz. depression of the white-cell count, with the rare development of agranulocytosis, and depression of blood platelets with, rarely, a purpuric state.

There are no reports, so far, of renal damage, but 2 deaths due to liver involvement have been reported lately.[16] In addition, one death has been reported showing a lesion indicative of interstitial myocarditis, which has been found in some cases of sulphonamide allergy.[17]

Mild headache, malaise and drowsiness have been recorded in a few patients when receiving the higher initial dosage of either BZ 55 or D 860.[13,15] Ridolfo and Kirtley[18] reported a case where mental clouding developed with a very high BZ 55 blood level. With reduced dosage the patient made a complete recovery.

Further, it has been shown that the uptake of radioactive iodine is reduced in patients treated with either drug.[19]

Up to the present, serious side-effects have not been noted with D 860. Very large dosage of D 860 has produced transient reduction in the polymorphonuclear leucocytes as the result of a maturation arrest.[18]

SUBJECTS AND METHODS

Forty-eight elderly diabetic out-patients were selected at random. The reason for the restriction of the investigation to this elderly diabetic group was that it has already been demonstrated that these preparations are of little or no use in the young diabetic.[5,6]

The patients were divided into 2 groups. The first group (A) of 14 patients was treated with BZ 55 and the second group (B) of 34 patients with D 860. Group B was later increased to 40 patients as a result of the transfer of 6 from group A to group B. Originally it was

TABLE I. NUMBER, AGE AND SEX OF PATIENTS, DURATION OF DIABETES IN YEARS AND TREATMENT

Treatment	*No. of Patients*	*Sex*	*Age (years)*	*Duration of Diabetes (years)*
BZ 55	14	M 4	50-71	1-12
		F 10	55-75	1-19
D 860	40	M 7	54-76	2- 7
		F 33	50-73	0-26

planned to treat 2 groups of equal size but reports of 3 deaths of patients treated with the standard dose of BZ 55 prompted us to discontinue placing any further patients on this drug while continuing it in a few cases which appeared to be responding well. Details of these

patients are given in Table I. Twenty-nine of the cases had been receiving treatment with insulin, the dosage varying between 10 and 110 units per day; in addition all patients were on strict diabetic diets.

Every patient had been followed for some time previously and fasting blood-sugar estimations had been done at intervals. In addition, on the day before treatment with the new drug was commenced blood-sugar determinations were carried out at 8 a.m., 11 a.m. and 3 p.m. A complete blood-count, blood-urea estimation, and a battery of liver-function tests were also carried out on most of the patients. The urine was examined for protein and sugar. The blood-pressure readings were taken in all patients and the fundi of the eyes examined in each.

The dosage of BZ 55 administered to patients of group A was 2·5 g. on the first day, 1·5 g. on the second day and 1 g. on each subsequent day. The whole dose was administered before breakfast each morning. The dosage of D 860 given to patients of group B was 3 g. on the first day, decreasing by 0·5 g. each day until a maintenance dose of 1·0 - 1·5 g. daily was reached. Here again the total dose was administered immediately before breakfast each morning.

During the course of the treatment patients were kept under frequent observation and were told to report immediately if any unusual symptoms occurred. They were particularly instructed to do so should any sore throat, rash or skin irritation occur.

Blood-sugar estimations were carried out from 1 to 3 times daily, and a complete blood-count was performed at intervals.

Patients have been kept on these drugs for variable periods of time, the maximum being 3 months. An attempt has thus been made to make a short-term evaluation of these drugs, particularly in view of the fact that D 860 is now appearing on the open market and that BZ 55 has been withdrawn by some manufacturers owing to its toxicity.

RESULTS

In order to demonstrate the blood-sugar lowering effect of D 860, blood-sugar determinations were performed on 2 patients on successive days at half-hourly intervals from 7 a.m. to 12 noon. The experiment was terminated at that time, when the patient was given his midday meal. On the first day specimens of blood were taken from the patient, who had been fasting from 9 p.m. the night before. No D 860 was given on that day. On the second day the experiment was repeated but the patient was given 3 g. of D 860. Fig. 1 shows the result of this experiment.

The patients have been divided into 3 categories: good, fair and poor (Table II). The 'good' category consists of those cases in which (*a*) insulin, where used, has been discontinued, (*b*) blood sugars have been maintained at normal or near normal levels, and (*c*) the patients are feeling well and there are no side-effects. The 'fair' category consists of those patients in which (*a*) insulin, where used, has been discontinued, (*b*) the blood sugar has not been maintained at normal levels but has been reduced appreciably, and (*c*) the patients

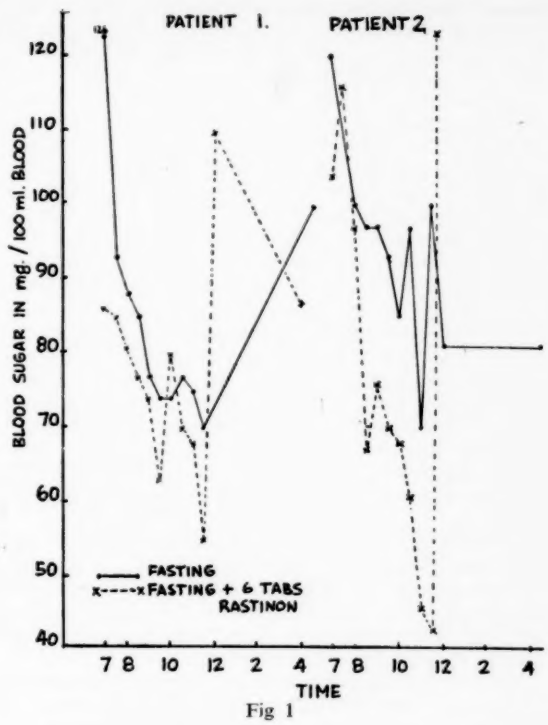


Fig 1

are feeling well and there are no side-effects. In the 'poor' category are those cases which have shown no improvement or very little.

TABLE II. RELATIONSHIP OF THE AGE OF THE PATIENT AND DURATION OF DIABETES TO RESULTS

		BZ 55			*D 860*		
Category		*No. of Cases*	*Average Age*	*Average Duration of Diabetes (years)*	*No. of Cases*	*Average Age*	*Average Duration of Diabetes (years)*
Good	M	3	66·6(60—75)	5(1—12)	M 4	60·5(54—75)	4(3—7)
	F	6	67·0(62—71)	5(1—19)	F 13	63·7(54—73)	3·9(0—19)
Fair	M	—	—	—	M —	—	—
	F	1	65·0	5	F 7	63·6(50—69)	7·1(2—17)
Poor	M	1	55·0	10	M 3	67·7(63—76)	4(3·4—5)
	F	3	55·0(50—61)	9·3(6—12)	F 13	60·3(50—70)	10·5(2—26)

First Category (good response)

Nine of the 14 patients (3 males and 6 females) on BZ 55 and 17 (4 males and 13 females) of the 40 patients on D 860 are included in this category. It was noted that the reduction of the blood sugar commenced within the first 24 hours of treatment being initiated and within 4 days the response was complete. Blood-sugar levels showed that the degree of control obtained by the use of the new drugs was better than that obtained by insulin, i.e. the fasting blood-sugar levels fell from 155 (78-284) to 114 (85-165) mg. per 100 ml. Some difficulty was experienced in deciding whether insulin should be discontinued simultaneously with the initiation of the new

treatment or whether this should be effected by a gradual reduction. While no hard and fast rule could be laid down it was found that where an amount of up to 20 units of insulin was being given, this could be discontinued immediately. Where, however, a larger dose of insulin was being administered it was thought to be safer to reduce the insulin by 5-10 units per day. However, it must be appreciated that in the first few days after the initiation of treatment, symptoms of hypoglycaemia may occur and a close watch must be kept on the patients during this period. It is felt that many more cases will have to be observed before it is possible to lay down a definite method for the substitution of this new drug for insulin. In our own cases symptoms of hypoglycaemia have been very mild, being found in 3 cases, all of whom complained of dizziness.

In the group of patients on BZ 55, 5 (1 male and 4 females) had never received any insulin; of the others (2 males and 2 females) the highest dose of insulin was 40 units per day. In 3 of these the insulin was withdrawn on the initiation of BZ 55 therapy, in the 4th (40 units per day) insulin was withdrawn in stages over a period of 4 days.

In the D 860 group 6 patients had not had any insulin. The insulin dosage of the 11 others (4 males and 7 females) varied from 10 to 60 units per day. In 5 cases (1 male and 4 females) insulin was withdrawn slowly over periods varying from 4 to 7 days. Sudden withdrawal was practised on the others.

It has been suggested that the best results are obtained in the obese type of diabetic and in those in whom the diabetes is of recent origin. In the BZ 55 group, 5 were obese (2 males and 3 females) and 4 of medium build (1 male and 3 females). In the D 860 group, 7 were obese (1 male and 6 females) and 10 of medium build (3 males and 7 females).

The relationship of the duration of diabetes to the response to these drugs is shown in Table II.

Second Category (fair response)

One female patient on BZ 55 and 7 female patients on D 860 are to be found in this category. Five of the patients on D 860 had received insulin before the new treatment was begun, the insulin dosage varying from 10 to 70 units. The fasting blood-sugar level in 2 patients on D 860 fell from 231 and 170 respectively to 178 and 131 mg. per 100 ml., but the levels rose slightly in the remaining 3 cases. The patient on 70 units of insulin was able to discontinue the insulin gradually over a period of 10 days and although the blood sugar is somewhat higher than it was on insulin, the patient is feeling well and the fasting blood-sugar does not exceed 150 mg. per 100 ml. Increase of dosage up to 2·5 g. per day of D 860 has not improved the results to date.

The patient on BZ 55 was of the obese type, as were 4 of the 7 patients on D 860.

The duration of the diabetic state in relation to response of this group is shown in Table II.

Third Category (poor response)

One male and 3 females on BZ 55 and 3 males and 13 females on D 860 belong to this category. Three (1 male and 2 females) on BZ 55 and 11 (2 males and 9 females) on D 860 were in receipt of insulin, the dosage varying from 15 to 120 units. In these patients there was poor response to treatment with the new drugs. In fact, the fasting blood-sugars rose in most cases to pre-insulin levels. Two of these patients were very labile diabetics in whom difficulty was always experienced in insulin control. The one, a male, was continually on the verge of either hyper- or hypoglycaemic coma while on BZ 55; the other, a female, could only be partially controlled by giving her half her usual dosage of insulin (lente insulin 20 units instead of 40 units) in addition to D 860. There appeared to be no advantage in giving both the insulin and D 860, and the patient reverted to her usual dose of lente insulin only.

The BZ 55 cases were all of medium build, as were also 7 of the D 860 group (1 male and 6 females). Eight (2 males and 6 females) were obese and 1 was thin.

The relationship of the duration of diabetes to the response to the new drugs is shown in Table II.

BZ 55 in relation to D 860

Six patients who were first treated with BZ 55 were later transferred to D 860. In no case was control found to be any better on the one drug than on the other. It was found that where the patient was on a maintenance dose of 1 g. of BZ 55 he could be kept under similar control on a dosage of 1 to 1·5 g. of D 860.

Side-effects

Mild dizziness due to hypoglycaemia occurred in 3 patients during the early stages of treatment with BZ 55. Nausea but no vomiting occurred in 2 patients on the same preparation. Several of the failures in both series stated that they felt 'out of sorts', being tired and listless. In 1 patient a subcuticular mottling and skin irritation occurred while the patient was taking 1 g. of BZ 55 per day. This condition subsided when the dosage was reduced to 0·5 g. per day and disappeared entirely when the patient was given 1 g. of D 860 daily in place of BZ 55. No reduction in haemoglobin, leucocytes or platelets was noted in the whole series. However, in a number of cases a reversal of the neutrophil/lymphocyte ratio occurred, but this returned to normal while the patient was still kept on the same dose of the drug, and it is therefore impossible to state that the drugs were responsible for the changes noted. No changes were found either in the blood-urea or liver-function tests.

Late Manifestations of Diabetes

The possibility that some of the patients showing late manifestations of diabetes[20] might give a different response to these drugs than those without such manifestations prompted us to undertake observations on the blood pressure, urine and eyes of these patients. The results were as follows:

Hypertension. In the patients showing a 'good response' to BZ 55, 1 male and 2 females had hypertension. In those showing a 'good response' to D 860, 5 patients, all females, had hypertension, the remainder having normal blood pressure. In the 'fair result' group, 4, all on D 860, had hypertension. Among the failures, 3 females on BZ 55 had hypertension, as did 5 females on D 860.

Proteinuria. Two patients (1 male and 1 female) showed proteinuria and both gave good results with D 860. In neither of these cases was the proteinuria increased during treatment and in none of the cases treated did proteinuria manifest itself.

Eye Changes. In the 'good' category 1 patient (female) on BZ 55 showed retinopathy, as did 1 female on D 860, and 2 females on D 860 had cataracts. In the 'fair' category 1 female patient on D 860 had cataract. In the 'poor' category 2 patients on D 860 showed retinopathy.

DISCUSSION

In the evaluation of a new preparation two questions call for answer: (1) Is it effective? (2) Is it safe?

The series of cases which we have presented suggest that in a proportion of diabetics in the older age-group both BZ 55 and D 860 are effective in controlling the blood sugar. Thus 9 out of 14 cases on BZ 55 and 13 out of 40 cases on D 860 could be effectively controlled without the aid of insulin for periods varying up to 3 months. Whether these preparations will ever take the place of insulin is still to be decided. It has already been found that the preparations are ineffective in the young diabetic and in those showing marked ketosis. In severe infections Stötter[8] has thought it advisable to give small additional amounts of insulin. Some workers prefer to discontinue these preparations and to revert to an insulin regime during intercurrent infections.

In complications such as surgical procedures a change to insulin has been recommended.[13]

It must be accepted therefore that both BZ 55 and D 860 are only of limited use in the treatment of diabetes. What remains to be determined is the safety of the preparations, over both short and long periods of administration.

Various workers have shown during the comparatively short period during which the drugs have been used that serious toxic effects can occur with BZ 55. Thus agranulocytosis, purpura and interstitial myocarditis have occurred, in addition to sensitivity eruptions. Lately 2 deaths have been reported from liver involvement. So far no serious effects have occurred as the result of the administration of D 860 which, it is suggested, is less toxic as a result of the slight change in formula from BZ 55. In view of the fact that the method of action of these drugs is not yet known it is essential that their use should be exercised only under strict medical control.

Some of the theories of the mechanism of action are worthy of note. Von Holt *et al.*,[21] in experimental work on rabbits and rats, found loss of the α cells in the pancreas when working with I.P.T.D; and this was confirmed by Loubatières *et al.*[22] Mirsky[23] has demonstrated that insulin activity is diminished by a high concentration of D 860 and that, as a result, the rate of destruction of insulin is diminished. He suggested, therefore, that the drug acted as an insulinase inhibitor. Vaughan,[24] as a result of experiments on rat-liver slices, suggested that D 860 may act by inhibiting one or more hepatic enzymes. Another theory suggests that these drugs stimulate pancreatic β-cell activity and thus increase the activity of insulin. In other words, it would seem that a great deal of work must still be done to elucidate the true action of these drugs.

The question of dosage is one which must still be worked out. While in the series of cases here reported the total daily dosage was given before breakfast, some of the German workers have tried using the drugs in divided doses during the day. Again, the dosage by Unger and Davidson[14] varies from 3 to 12 g. of D 860 per day. Here again we feel that we should be more certain that no toxic effects will occur with this larger dosage before using it to any extent. Incidentally, it may be mentioned that unlike other members of the sulphonamide group neither BZ 55 nor D 860 has given rise to crystalluria.

While some have suggested that the best effects with both these preparations are obtained in the obese type and in those cases where the diabetes is recent in origin, our own findings would suggest that this is not necessarily the case. Thus only 7 out of the 17 D 860 patients in the 'good response class' fell into the obese group, and only 5 out of 9 on BZ 55. Moreover, patients with diabetes of 7, 8, 9, 12 and 19 years' duration responded favourably to the action of the new drugs.

From the evidence so far obtained it would appear that we are fully justified in recommending a further extension of the trial with D 860. More work is required to determine whether any ill-effects occur, particularly on the liver and kidneys, both in experimental animals and in human beings, when the drug is used over a prolonged period of time. Until such long-term evaluation has been carried out, it is recommended that the drug should be used only when strict clinical and laboratory control is available.

SUMMARY

1. BZ 55 and D 860 are new oral anti-diabetic drugs.
2. Fourteen patients were treated with BZ 55 and 40 with D 860.
3. Thirty-four patients responded to treatment well or fairly well, and 20 patients did not respond to treatment.
4. Few side-effects were observed, although certain serious effects have been noted in the literature.
5. BZ 55 and D 860 were equally effective in a small number of cases.
6. D 860 up to the present has not caused the serious complications noted with BZ 55.
7. The effectiveness and limitations of BZ 55 and D 860 in the treatment of diabetes mellitus are discussed.

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A CLINICAL TRIAL OF D 860 (RASTINON) IN DIABETES

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A brief summary of the history of trials of oral preparations for diabetes mellitus has recently been given in this *Journal* together with a preliminary consideration of the use of carbutamide (BZ 55).[1, 2] This drug is already obsolete. It was too dangerous. Aside from rather frequent skin eruptions (about 9% affected) it occasionally produced severe agranulocytosis. The newer substance, D 860 (tolbutamide, Orinase or Rastinon) differs from BZ 55 simply in the substitution of a methyl group for an amino radical:

BZ 55—N-sulphanilyl-N^1-butyl urea—
$NH_2 \langle\rangle SO_2$. NH. CO. NH. C_4H_9

D 860—N-(4 methyl-benzene sulphonyl)-N^1-butyl urea—
$CH_3 \langle\rangle SO_2$. NH. CO. NH. C_4H_9.

This small difference in chemical structure abolishes the antibacterial action of BZ 55 and apparently also abolishes any untoward effect on the bone marrow, while allowing retention of the blood-sugar lowering potentiality.

Action of D 860

The mode of action of D 860 (presumably the same as that of BZ 55) is still uncertain. The original idea that it inhibited pancreatic alpha-cell activity is apparently incorrect,[3] but there are at least 3 other possibilities; it may actually stimulate insulin secretion, it may slow up insulin destruction by inhibiting insulinase,[4] or it may depress the release of glucose from the liver.

Whichever may be correct, it certainly has little or no effect in insulin-deficient diabetes, in which the pancreatic beta-cells are incapable of producing any endogenous insulin at all.

REPORTS TO DATE

At the time of writing the only comprehensive report available to the authors comes from Germany,[5] where workers summarize their results with 781 patients. Preliminary communications have also come from the U.S.A.[6-9] and Canada.[10] Unfortunately many of the latter accounts are spoilt by BZ 55 and D 860 having been used together and reported on indiscriminately. It should not be assumed that the two drugs act in exactly the same way.

Type of Patient Treated

As with BZ 55, so with D 860, the literature makes it plain that the 'young severe' diabetic will not respond. The drug, therefore, should not be used in this type of case, except experimentally. The German authors[5] claim that the obese patients (including those with Cushing's syndrome) respond best. They found a clear correlation between age and response; over the age of 40, 50% or more of their patients could be stabilized on D 860. Similarly there was a close correlation between response and the age of onset of the diabetes.

The same authors found no clear relationship between the length of time the diabetes had been present and the response to D 860. This differs from the reports from Germany on BZ 55, which indicated a more favourable outcome in diabetes of recent onset.

According to the same group of workers, the larger the dose of insulin in use before D 860 was tried, the less likely was the patient to respond; while a similar negative correlation was found between the patient's

response and the length of time during which insulin had been used.

The presence of diabetic vascular 'complications' seemed to make little difference to the likelihood of response to D 860, except that patients with retinopathy as a sole symptom did badly. The reason for this is obscure—unless this group contained a very high proportion of the 'young severe' type of diabetic. Certainly retinopathy is not suggested as a contra-indication to the use of D 860. Indeed, the older patient with advancing retinopathy may be just the person in whom a more accurate stabilization of a mild diabetes with D 860 will be valuable.

Side-Effects

Body Weight. The German authors reported a close correlation between increasing body-weight and response to D 860; the drug itself, however, appeared to have no particular effect on weight.

Lipoid Metabolism. The Americans have been unable to produce a fall in serum cholesterol with D 860,[6] and it is plain that this deficiency may prove to be a serious drawback to long-term therapy. On the other hand one group of German authors claim to have found a fall in total lipoids and in cholesterol.[5]

Subjective Complaints. Occasional euphoria and depression have been reported; also headaches from excessively high doses. Constipation was sometimes caused.

Intestinal Flora. No change was found.

Renal function was unchanged. It should here be noted that the excretory product of D 860 is precipitated by acid, and consequently gives a false positive test for albumen with the sulphosalicylic and the Esbach reaction (but not with the boiling test).

Liver functions remained unimpaired in normal patients and were not aggravated in those with cirrhosis, regardless of dose and length of therapy.

Rashes. Occasional urticarial eruptions have been reported (about 1% of subjects). These are much less common than with BZ 55 (about 9% of subjects), and usually disappear even if the drug is continued.

Blood Cells. Absolutely no depression of any of the blood cells has been found. In particular no cases of agranulocytosis—nor even of leucopenia (possibly one case)—have been recorded.

Alcohol. One person is reported to have become abnormally sensitive to alcohol while on D 860. Possible medico-legal complications should be remembered.

Hypoglycaemia is far less easily produced than with insulin. Nevertheless prolonged and dangerous hypoglycaemia seems occasionally to occur from very large doses, especially if insulin is also being used.

Dosage

D 860 is cumulative when given in daily doses. Consequently the usual practice is to start with a large dose (2-3 g.) and reduce gradually to a maintenance of 0·5-1·5 g. Occasional patients have been found in whom larger doses (up to 6 g. per day) have been necessary to produce improvement in carbohydrate metabolism. The latter dosage should be used only in strictly controlled circumstances and is still largely experimental.

Discontinuance of D 860

After stabilizing a diabetic on D 860 for a period, the effect of discontinuance has been observed. Sometimes the carbohydrate tolerance does not apparently deteriorate for a matter of weeks, but in every case D 860 or insulin therapy has eventually had to be resumed. A *cure* is, therefore, never to be expected.

Rapid Tests for Suitability of Individual Patient

Oral and intravenous D 860, followed by serial blood-sugar estimations, have been used in order to try to assess the response of the individual patient to routine D 860 therapy.[9] So far these trials have been, in our opinion, unconvincing and, until further evidence is forthcoming, the only way to know if a diabetic will respond well to D 860 therapy is to try it. This statement is subject to the proviso that the severe, growth-type, ketosis-prone diabetic will certainly not respond.

Long-Term Results

Most patients reported in the German articles have remained satisfactorily stabilized on D 860. In a few, however, the control deteriorated, and either a raised dose of D 860, or insulin, became necessary.

PRESENT SERIES—I. OUT-PATIENTS

Methods

A total of 64 patients comprises the series on whom D 860 has been tried in the diabetic clinic. These patients have been seen weekly as far as possible and control has been checked by regular blood-sugar examinations (usually fasting, capillary blood; each test under the same circumstances for each individual). Weekly 24-hour urine collections have been analysed for glucose in some cases; in others a note has been made by the patient of their own tests through the week; in a few, repeated glucose tolerance tests have been carried out. Total white-cell counts and serum cholesterol have been recorded in some.

The dosage of D 860 was in most cases the standard one of 3 g. the first day, reducing to 2·5, 2, and then continuing with 1 g. per day. A few patients received higher doses, and in a few a reduction to 0·5 g. daily was tried. The tablets were taken in divided doses, although there are no grounds for believing this to be necessary.

The change-over to D 860 in a patient on insulin was accomplished in various ways. If response was thought unlikely and the patient was severely diabetic, the insulin was not completely discontinued; on the other hand whenever no risk was considered to be involved the insulin was stopped for some 3 weeks before D 860 was used. In this way a real base-line control could be established and, furthermore, several patients could be picked out who really did not need insulin or D 860 at all. (This was also found by Creutzfeldt and Schlagintweit.[5])

It must be emphasized that our findings concern short-term therapy; D 860 has been available to us for only 4 months.

Results

Age. Of the 64 patients 57 were between 40 and 80. No patient in this series under 40 years of age responded satisfactorily to D 860 (4 of the 5 between 20 and 40 were, however of the severe type). The one patient over 80 also did not respond. The only patient under 20 was made symptomatically worse and showed an increased swing of blood sugar with spikes of hypoglycaemia.

Type of Diabetes. Before analysing our results further it seems to us essential to separate off the severe ('growth-onset', ketosis-prone, insulin-requiring) diabetic from the mild ('maturity-onset', frequently obese) group. We found it necessary to consider a third group, of intermediate severity, the members of which were in the older age-group but developed severe diabetic symptoms with marked weight-loss (though without ketosis) and needed insulin. There were 12 patients in the severe and intermediate groups. Three of them (all 'intermediate') responded very well and were controlled on D 860 only (eg. Fig. 1). In the others, D 860 produced no discernible effects apart from the deterioration of control in the young girl referred to above. As far as we could judge from the limited out-patient data, of the 52 'mild' cases on standard doses of D 860, the control achieved in 8 cases (15%) was excellent, in 30 (58%) it was partial† (e.g. Fig. 2), and in 19 (37%) there was no response at all (Table I).

TABLE I. TYPE OF DIABETES AND CONTROL WITH D 860 (WHOLE SERIES)

	Excellent Control	*Partial Control*	*Negligible Control*	*Total*
Severe	0	1*	5	6
Intermediate ..	3	1	7	11
Mild	9 (15%)	31 (56%)	16 (29%)	56
Total	12	33	28	73

* plus insulin.

Sex. There were only 9 males with 'mild' diabetes in the series, but it was surprising to find that 7 of these failed completely to respond to D 860 (Table II), while of the 43 females 35 responded. Such a result has not been previously reported and, while these preliminary figures look striking, we are very doubtful whether they will prove significant in the long run. Statistics show that such a difference is very unlikely to occur from pure chance (the difference between the percentages of males and females responding to D 860 being 3 times its standard error).

TABLE II. SEX AND CONTROL WITH D 860 IN MILDLY DIABETIC OUT-PATIENTS

	Excellent Control	*Partial Control*	*Negligible Control*	*Total*
Male	—	2	7	9
Female	8	27	8 (19%)	43
				52

Length of Diabetic Period. Of our 'mild' diabetics 6 had had their disorder for more than 10 years. Of these, 4 failed completely to respond to D 860. This does suggest (as stated with BZ 55[1, 2]) that the outlook is less favourable with long-standing diabetes.

Body Build. We have divided our 'mild' diabetics into 3 groups, obese, medium and thin. Table III shows no difference in response between the 3 groups. The German authors state that they found obese patients to respond better, but they did not separate the 'severe' diabetics from the 'mild' ones, and since virtually all the 'severe' ones are non-obese, their figures became loaded and hence invalid for consideration of the prognosis of the mild, non-obese diabetic. Our results are satisfactory, since it is the mild lean diabetic who especially needs 'tablet' therapy, as opposed to the obese patient, who needs dietary restriction.

TABLE III. BODY BUILD AND CONTROL WITH D 860 IN MILDLY DIABETIC OUT-PATIENTS

	Excellent Control	*Partial Control*	*Negligible Control*	*Total*
Obese	2	10	6	18
Medium	4	15	9	28
Thin	2	3	0	5

Prior Insulin Treatment. Of the 52 'mild' diabetics 17 were taking insulin up to the time of the trial of D 860, and in all cases it was omitted before the tablets were started. The control achieved on D 860 was excellent in 4, it was partial in 8, and 5 derived no benefit. In all the 12 who responded, D 860 produced better control than the previous insulin had done.

Comparison with Carbutamide (BZ 55). We can use our results to compare BZ 55 with D 860 in 2 ways. First, by the total percentage response of mild cases as out-patients: With BZ 55, 25 out of 28 patients responded well (89%); with D 860, 37 out of 52 (71%). Of course, the composition of the 2 groups was not balanced, so that the figures are not entirely comparable. Secondly, we can compare the result of the 2 drugs given consecutively in the same patient in the same dosage. This has been done on 28 mild diabetics and, as far as possible, repeated trials with one drug after the other have been made. In 20 cases there was no definite difference between the effects of BZ 55 and of D 860. In 6 there was distinctly better control on BZ 55 (see Fig. 3) while in 2 it was better on D 860. We therefore have the impression that D 860 is somewhat less active than BZ 55, but that this lesser activity is not of sufficient degree to constitute a serious drawback.

Side-Effects. One patient complained of tiredness and one of nausea while on D 860. In both cases BZ 55 produced better control of the diabetes and did not occasion these symptoms. Otherwise we saw no toxic effects whatever—in particular no fall in the leucocyte count and no rashes. Hypoglycaemic attacks did not occur (except possibly in 'A', Fig. 4). In the few cases in which the serum cholesterol was repeatedly estimated, no change was observed during D 860 therapy.

Free Diet. As discussed in a previous communication,[2] we see no reason for restricting diet in a diabetic who can be well controlled on oral therapy and who is

† By 'partial' we mean that the blood sugar did not become normal, or that some glycosuria persisted; the control achieved, however, was often satisfactory.

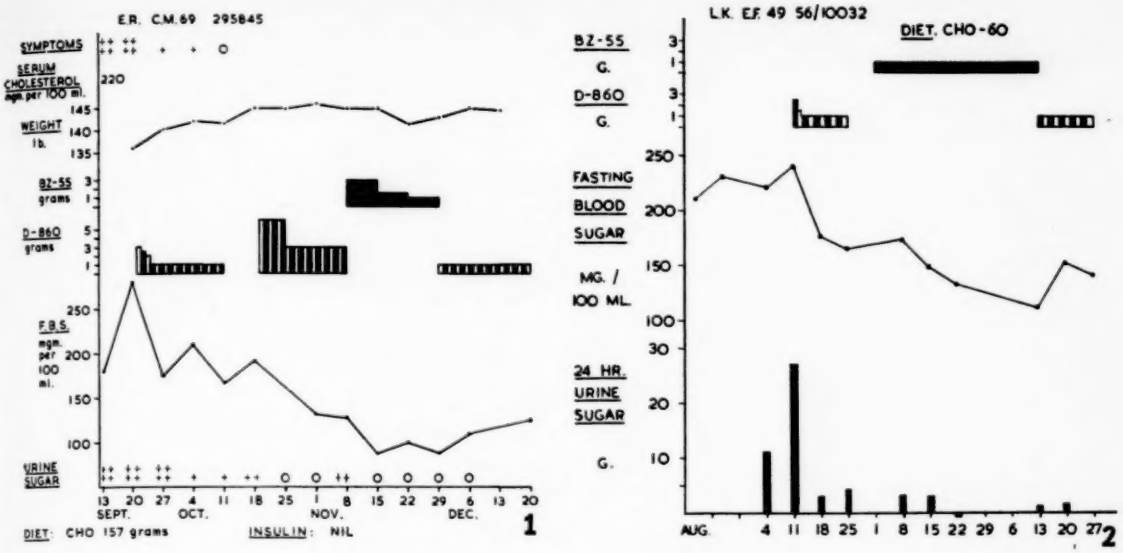

Fig. 1.* Diabetic of intermediate severity and recent onset. Symptoms were severe. Note improvement on standard doses of D 860, with some weight gain and further improvement on large doses. Blood sugar further lowered by BZ 55, and control maintained on standard doses of D 860.

Fig. 2. Mild diabetic of 4 years standing, poorly controlled on diet only. Note improvement on D 860, but possibly greater effect of BZ 55.

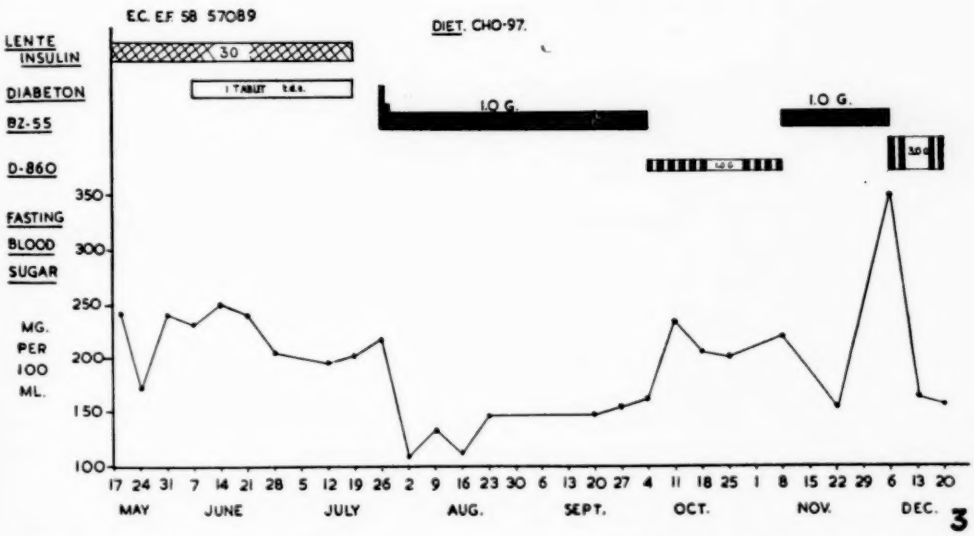

Fig. 3. Mild diabetic for 5 years, previously taking small doses of insulin. Off insulin, the diabetes was better controlled by BZ 55, which was distinctly more effective than D 860, in the same dosage. Larger doses of D 860, however appeared more effective.

* Note to all figures: 'C.M.' indicates coloured male etc. 'CHO-97' indicates a diet containing 97 g. of carbohydrate. *Absence* of any sugar in a 24-hour urine is shown by a small bar *below* the base line.

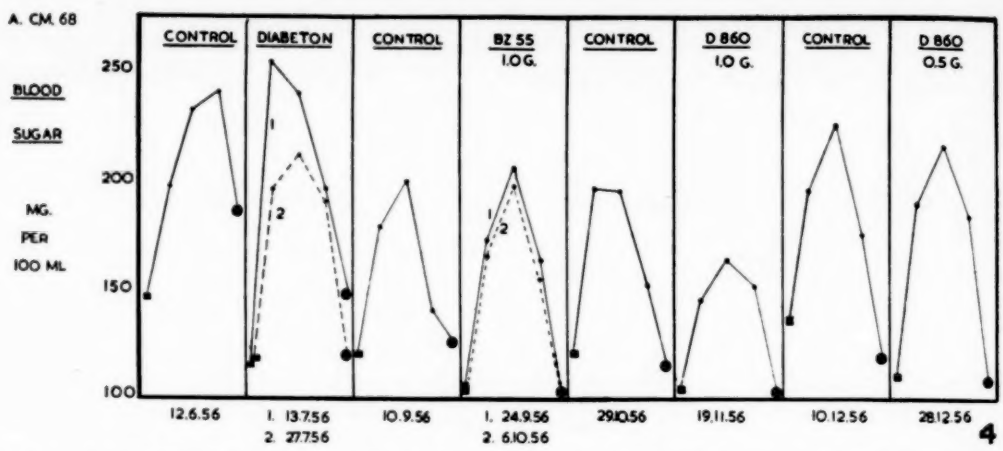

Fig. 4. A mild diabetic who was followed up by repeated glucose tolerance curves. 'Diabeton' was inactive. BZ 55 most interestingly reduced the fasting and 2-hour sugar levels, while the intervening ones were still abnormally high. The only quite normal curve was achieved on D 860, 1 g. daily; 0·5 g. does not appear to be as effective. (Note: points on each curve represent half hourly readings. ■ indicates fasting levels and ● the 2-hour levels.)

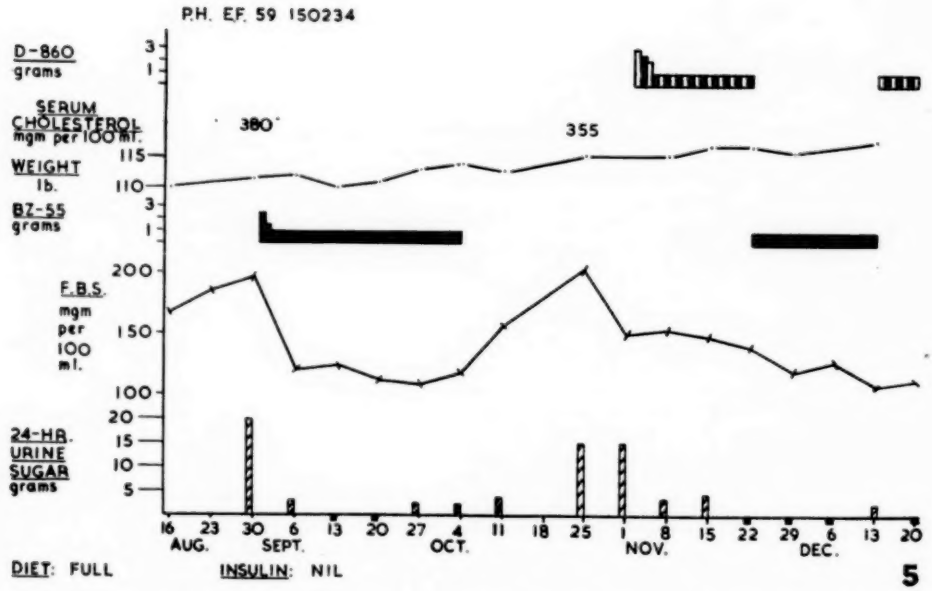
P.H. EF. 59 150234
D-860 grams
SERUM CHOLESTEROL mgm per 100 ml.
380
355
WEIGHT lb.
BZ-55 grams
F.B.S. mgm per 100 ml.
24-HR. URINE SUGAR grams
16 23 30 6 13 20 27 4 11 18 25 1 8 15 22 29 6 13 20
AUG. SEPT. OCT. NOV. DEC.
DIET: FULL
INSULIN: NIL
5

Fig. 5. A thin woman, mildly diabetic for 5 years, previously taking small doses of insulin. Control improved by BZ 55, relapsed after discontinuation, again improved by D 860, though BZ 55 may have been somewhat more effective. Actually the tolerance curves on both oral drugs are grossly abnormal, despite a lowered fasting level. Note the weight gain on free diet.

under-weight. In this series we encouraged these patients to eat 'everything'. In 2 we obtained good control on D 860, and in the other 2 the control was excellent; 3 have gained weight on this regime—something they had been quite unable to do for years previously (e.g. Fig. 5).

Effect of Withdrawal of D 860. All patients who were controlled on D 860 relapsed after its withdrawal. In some, however, the relapse was virtually immediate while in others it did not occur for a few weeks. A lasting effect or 'cure' from D 860 does not appear to have been claimed by any workers.

Use of Large Doses. Doses of 3 g. per day or more were used in 6 out-patients:

1. A moderately obese woman of 59, whose diabetes was of 10 years' duration and who had been taking 50 units of insulin daily. Taken off insulin, her fasting blood sugar was around 280 mg. per 100 ml.: the urine sugar was 2-3 plus. Standard doses of D 860 and BZ 55 had no effect, but D 860 in 3 g. doses reduced the fasting sugar (readings of 162, 185, 100 and 201) and the urine sugar.
2. A mildly diabetic man of 62, average build, diabetes of about 24 years duration, taking 35 units of insulin daily. D 860 in doses up to 4 g. daily did not effect good control without insulin.
3. A severely diabetic woman of 23 obtained no benefit from D 860 in doses of 3 g. daily. This, with 14 units of insulin (half her regular dosage), was insufficient to effect control.
4. A male of 36, with recent 'intermediate' diabetes, was not controlled with doses up to 6 g. of D 860 daily, though 20-30 units of concurrent insulin sufficed.
5. A man of 50 with chronic pancreatitis and recent mild diabetes was controlled quite well on 6 g. and then on 3 g. of D 860.
6. A Coloured man of 69 with recently discovered diabetes of intermediate severity was well controlled on 6 g. a day, and maintained on 3, 1·5, and now 1 g. only (Fig. 1).

PRESENT SERIES—II. IN-PATIENTS

Methods

In-patients were chosen to include diabetics of diverse types, especially the severe and intermediate groups. Large doses of D 860 were often used. Because of the reported tendency for the oral drugs to reduce blood sugar in the fasting state more strikingly than post-prandially, most of the bloods were drawn after breakfast at 10.30 a.m. In this way we hoped to see whether D 860 could effect more complete control. Analysis for total glucose content was made of 24-hour urine collections. Twelve patients were considered worth including for discussion.

Results

Severe Diabetes

1. M.M., Native female, 24 years old (25178). A severe unstable, brittle diabetic of 6 years duration, passing about 100 g. of glucose daily on 50 units of mixed insulin. She was given 6 g. of D 860 daily, in addition to the insulin, for 15 days, which produced no evident effect whatever.
2. B. v.d. P., European female of 25 years (56/01931). An unstable diabetic of 1 year's standing, badly controlled on 40-50 units of insulin daily. The addition of D 860 (3 g. daily) to the insulin reduced the urine sugar from around 150 g. a day to 20-30 g.; the blood sugar, however, swung between 400 mg. and hypoglycaemia.
3. A.P., — year-old Coloured male (55/20963) with recently discovered diabetes, arrived in hospital completely uncontrolled on 15 units of lente insulin. To this was added D 860, in doses from 6 g. up to 12 g. daily, for a period of 14 days. There was no observable effect.

Intermediate Diabetics

4. J. W., European female of 58 years (42315), a known diabetic for 16 years, moderately well controlled on 70 units of lente insulin and quite out of control on diet only. D 860 in doses of 3 g. daily was without effect.
5. S.L., Coloured female of 50 years (100386), diabetic for 8 years, somewhat obese, was insulin-resistant. She was really no better controlled on 100 units of lente insulin than on no insulin at all. Without insulin, D 860 in standard doses was without effect. In doses of 2·5 g. daily the urine sugar was reduced from about 20 g. to about 6 g. a day, but the fasting blood-sugar was unchanged. Her renal threshold was found to be 220 mg. per 100 ml. Possibly the change in the threshold was due to the action of the D 860.

Mild Diabetics

6. B.C., a thin European female of 83 years (96772), diabetic for 30 years, had been treated by diet only for the previous 10 years. On standard doses of D 860 her urine sugar of 10 g. per day was halved, although the fasting blood-sugar was little affected. On continuation as an out-patient, however, the blood sugar was drastically reduced, and the urine remained sugar-free, despite the establishment of a full diet, upon which the patient's weight rose from 88 to 99 lb. in 1 month.
7. I.M., Coloured male of 80 (56/29562), with mild, newly discovered diabetes. D 860 had little or no effect, except for some reduction of fasting blood-sugar.
8. C.B., European female of 60 years (56/10681), diabetic for 26 years, moderately obese. On a restricted diet, D 860 had no definite additional effect.
9. M.R., male, aged 51 (171789), of average build, diabetic for 8 years, previously on 24 units of lente insulin. D 860 in standard doses produced partial control, probably satisfactory for continued therapy.

Chronic Pancreatitis (with calcification of pancreas)

10. J.F., European male aged 35 (55/12496), with unstable diabetes of 11 years' duration and taking 80 units insulin daily. Without insulin, D 860 in doses of 6 g. daily did not reduce the urinary output of sugar below 160-200 g.
11. W.W., European male aged 56 (8998), unstable diabetes for 4 years. D 860 added to 20 units of lente insulin was without effect (3-day trial only).

Thyrotoxicosis

12. J.C., thin European female of 46 years (56/12926) with diabetes of recent onset, could not be controlled by standard doses of D 860, nor did this appear to help substantially in the control afforded by 40 units of lente insulin.

Toxic Effects. None were seen, even from the large doses.

DISCUSSION

Patients over 80. Of the 3 patients over 80 years old in the whole series, all with mild diabetes, it is interesting that 2 did not respond to D 860 at all, the other one only partially. In the 2 who did not respond the diabetes was of recent onset.

Chronic Pancreatitis. We have used D 860 in 4 patients with chronic pancreatitis. In 3 it had no effect at all. In one patient the diabetes was recent and unusually mild, and here it did seem to help. It looks as if the typical unstable diabetes of chronic pancreatitis, which requires large doses of insulin, will not be benefitted by D 860.

'*Complications*'. We have not really had enough experience to say anything of the effect of diabetic 'complications' on the likelihood of control by D 860. Retinopathy, neuropathy and nephropathy have been encountered both in patients who did well and in patients who did badly. During non-specific stressful

complications, such as severe infections or a major operation, insulin should be used as it would have been before the advent of D 860.

Value of fasting blood-sugar estimations. We have seen patients on D 860 in whom the fasting blood-sugar has come down to normal, yet whose post-prandial blood sugar and urinary sugar remain high. Too much reliance, therefore, should not be placed on the fasting sugar as the sole test of response to D 860.

CONCLUSIONS

It is plain that D 860 is a valuable substance of considerable potency in some diabetics, and blessed with a remarkable lack of toxicity. The effectiveness is largely limited to the mild, 'maturity-onset' diabetic, whether fat or thin. As we remarked, however, when considering BZ 55, we do not believe that it should be used as a short cut to stabilization of the carbohydrate metabolism in an obese patient. These people need dieting for their obesity—in fact this obesity is the primary disease rather than their diabetes, and must be treated as such. Hence we conclude that the place for D 860 at present is in the treatment of the non-obese mild diabetic, in whom it may be a boon by (1) controlling the diabetes better, (2) allowing cessation of insulin injections, and (3) allowing a more liberal diet.

Since D 860 is now available for retail purchase a warning should be sounded. It may be very dangerous to stop insulin and use D 860 in its place. In fact we believe that in no patient should insulin be discontinued without expert or hospital supervision. It follows from this that the sale of D 860 should be controlled, and that it should be available to the public by prescription only.

SUMMARY

The properties of the substance, D 860 (Rastinon) are briefly reviewed, and followed by a consideration of the clinical work so far reported. The latter has come mainly from Germany, although it is known that large-scale trials are under way in other European countries and in the USA. The German authors found that the mild obese diabetic responded best, but we take pains to state our belief that a low-carbohydrate, low-calorie diet must remain the basis of treatment for such a person. Methods of employing D 860 and its pleasing freedom from toxic effects are noted.

We present our own preliminary findings in 64 out-patients and 12 in-patients. We have found a fair proportion of mild diabetics to respond satisfactorily to D 860, whether thin or fat. In fact we believe that there is a special place for D 860 in the non-obese and even the over-thin middle-aged diabetic. In the severe diabetic the use of D 860 must be considered as experimental only.

We further discuss our findings under various other headings, particularly its relation to insulin therapy, the comparison with carbutamide (BZ 55) and the use of large doses. We must finally emphasize that we do not know the results or the effects of long-term therapy.

ADDENDUM

We thank all physicians and other members of the staff for their assistance; in particular Dr. P. Markman.

The cost associated with this work was defrayed by grants from the Staff Research Fund of the University and from the Council for Scientific and Industrial Research.

The Rastinon (D 860) used in these tests was supplied by the Newport Trading Corporation of Johannesburg, to whom we extend our sincere thanks.

Since submitting this paper we have seen a large symposium from America[12] on the action and use of D 860. In general the results obtained seem better than our own, but it is notable that larger maintenance doses (2-3 g. daily) were frequently used as a routine.

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AN UNUSUAL CASE OF APPENDICITIS

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Rehoboth, South West Africa

A case of appendicitis is presented, where a goat's hair entered the appendix, passed along its lumen and penetrated the tip to lie free in the peritoneal cavity without causing any appreciable inflammatory changes.

A young European girl, aged 18, was brought in from a farm 90 miles away, complaining of a pain in the right iliac fossa. She had had this pain for a few weeks already and it got neither better nor worse. Her parents thought it was 'an appendix', and decided to seek medical advice. The pain was colicky in character, localized to the right iliac fossa, was only present at intervals, and was associated with nausea at times but never with vomiting; she was rather constipated. There were no gynaecological symptoms.

On physical examination she was found to be a well built young woman, not anaemic; the temperature, pulse and blood pressure were normal, and she did not appear to be in great pain. On palpation there was moderate tenderness over McBurney's point, no rebound tenderness and no paraesthesia or hyperaesthesia. The psoas and obturator signs were negative. The tongue

was clean and the breath was not offensive. General examination revealed nothing abnormal. Her previous history was that she had suffered from brucellosis some years before and that she had headaches at intervals.

Urine examination revealed nothing abnormal. Blood count: Haemoglobin 15 g.%, white blood-cells 10,000 per c.mm. (neutrophils 51%, lymphocytes 46%, monocytes 3%). In view of the previous history and the relative lymphocytosis a blood sample was sent away for brucella agglutination tests.

The differential diagnosis was considered to be between chronic appendicitis and brucellosis. The patient had meanwhile been admitted to hospital for observation, but no medication was prescribed except an enema, which produced a good result but had no effect on the pain. From the 2nd day the pain decreased and was completely gone by the 4th day, when the result of the agglutination tests came back negative. A definite diagnosis of chronic appendicitis was then made, but it was thought that appendicectomy was not justifiable under the circumstances and she was discharged.

Two months later a telephone call came to say that she was on her way, and would we please prepare for an appendix operation! This time the picture was essentially the same, but the pain was worse than before, as was the tenderness, the pulse was up to 98 beats per minute and the temperature was 99·5°F. A blood count showed an interesting change: Haemoglobin 14·8 g.%, white blood-cells 12,500 per c.mm. (neutrophils 84%, lymphocytes 15%, monocytes 1%). It was decided to operate.

A classical incision for appendicectomy was made; the omentum was not in sight, there was no excessive free exudate and no adhesions. The appendix was easily found and delivered with the caecum into the wound. The appendix appeared to be only very slightly inflamed near the tip, and something white and threadlike was protruding at the tip. The appendix was then wrapped in wet gauze and the said object pulled out with dissecting forceps—it came out very easily. On closer inspection this proved to be a goat's hair, the one half white and the other black, and about 1 inch in length. The appendix was thereupon closely inspected at the tip for any sign of gangrene, but there was none—in fact it was nearly normal, being only slightly injected. The appendix was then amputated and the operation completed in the usual way. The patient made an uneventful recovery and was discharged on the 7th post-operative day. She is now well and completely relieved of her symptoms.

DISCUSSION

Here then was a case where a goat's hair, which had most probably been swallowed with cooked goat's meat, had found entry into an appendix and had set up muscular spasm with resultant colicky pains, but practically no following inflammatory reaction at all. Muscular action had probably driven it further down the lumen of the appendix, still without any appreciable (naked eye) inflammatory changes. Probably because of its shape and size it had not caused any pressure necrosis of the appendicular wall. This stiff object had apparently cut through the tip of the appendix like a stilette without causing much upset in its anatomy or physiology.

But why were signs and symptoms so slight, taking into consideration that the appendix had been penetrated by a foreign object that must have been an irritant to the peritoneal cavity? Would one not expect a much severer peritoneal reaction? Possibly this would have developed if surgical intervention had been longer delayed.

GOUT—ITS NATURE AND TREATMENT*

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Gout has been a subject of speculation for centuries. There is no disease which has been more thoroughly studied or about which there is more uncertainty than the gout. The clinical manifestations have been thoroughly described and the metabolism repeatedly studied. Many theoretical questions have remained unsolved until recently but in the last 20 years substantial progress has been made in the understanding of this disease.

It has been recognized for over a century that gout ran in families, but the pattern of inheritance has never been clearly recognized. Multiple cases in one family were known to occur frequently but, on the other hand, isolated cases without affected relatives were also quite common.

Gout has long been recognized as due to faulty uric-acid metabolism and gouty patients have long been known to have hyperuricemia†. Isolated observations had been reported of relatives of gouty patients who had asymptomatic hyperuricemia. Talbott[1] was the first to investigate this phenomena and he discovered that 25% of the relatives of gouty patients had hyperuricemia. The thought occurred that it might be wise to investigate the heredity of idiopathic hyperuricemia and see what relation it had to gout. A study[2] was planned to make uric-acid determinations on as many relatives of gouty patients as possible. Furthermore, assuming that an appreciable proportion of relatives of gouty patients had hyperuricemia, it seems fair to assume that an appreciable part of the population had idiopathic hyperuricemia. The survey was expanded to include the general population. Uric-acid determinations were made on 224 gouty patients and their relatives and 1,024 tests on 961 patients, members of the general population.

NORMAL URIC-ACID LEVELS

Because of the importance of recognizing a definite level between hyperuricemia and normal it seemed desirable to determine the dividing line to be used in this study from our own experience of 1,272 tests. These included 248 tests on 41 gouty patients and 159 of their relatives or spouses and 1,024 tests performed by routine on 961 patients in the medical wards of

* A paper read at a meeting of the Cape Midland Branch of the Medical Association of South Africa, Port Elizabeth, 24 September 1956.

† American spelling retained throughout.

Cleveland City Hospital. All determinations used in this study were made by one individual using Benedict's direct method, and read with a Klett electric colorimeter on serum separated from clotted blood. Specimens were collected under oil without regard to fasting.

Data show a natural division of high and low levels between 6·4 mg. and 6·5 mg. A marked preponderance of determinations in gouty or hyperuricemic individuals fall above this line. A marked preponderance of tests of non-gouty individuals fall below this line. Thus in 77 tests upon 41 patients with gout, all but 3 are 6·5 mg. or more per 100 c.c. Of 23 determinations on 17 relatives considered to have hyperuricemia, only one was below 6·5 mg. In these two groups of hyperuricemic individuals, uric-acid levels were above 6·5 mg. in 96, or 96% of the tests.

Of 1,024 tests on 961 patients in the medical wards, 965 were below the level of 6·5 mg. Of the 59 above this value, 25 were on patients with nitrogen retention, a condition expected to produce hyperuricemia. Thus, only 34 or 3% of the tests showed an unexplained value above 6·5 mg. which might have been due to idiopathic hyperuricemia. As a result of these observations, and in the absence of evidence to the contrary, a serum-uric-acid level of 6·5 mg. or over per 100 c.c., was tentatively accepted as hyperuricemia or proof of gout.

The validity of this line of distinction between normal and hyperuricemia was tested statistically. A group of 294 normal females of the hospital population gave a mean uric-acid level of 3·63 mg. per 100 c.c. with a standard deviation of 1·06 mg. per 100 c.c. The mean for a similar group of 296 normal males was 3·95 uric acid per 100 c.c. with a standard deviation of 1·15 mg. per 100 c.c. The difference in the means is 0·32, a significant difference which one could expect as a result of random sampling only about once in more than 15,000 trials. The average uric-acid concentration for males is 1·088 times that for the females, which curiously enough agrees very closely with the differences between the sexes in physical stature as determined many years ago by Galton, and also with the difference in the figure usually taken as the average cranial capacity—1,200 c.c. for females, 1,300 c.c. for males.

To cut off the normal curve in the plus direction at 2 times the standard deviation brings the upper level of normality for males to 6·25 mg. and allows about one man in 50 to stand above that level who still might be regarded as normal. If it is desired to reduce this figure to one in 100, then the level of demarcation in round figures could be placed at 6·50 mg., 2·22 times the standard deviation above the mean. A similar estimate for females is 5·98 mg. It is interesting to note that in the sample of 294 normal females there were 2 who showed 6·0 mg. or more per 100 c.c. These values—6·5 mg. for males and 6·0 mg. for females—are, then, taken as the upper levels of normality for purposes of this study.

URIC-ACID LEVELS IN GOUT

In this study of 52 gouty individuals and their relatives hyperuricemia was found in 18% of 11 mothers, 17% of 24 brothers, 21% of 24 sisters, and 15% of 33 sons. Not a single daughter among 45 tested showed hyperuricemia. There was no correlation between age and uric-acid levels in males but a significant correlation was found among females. Since no female relative under the age of 50 was affected it seems possible that normal menstrual function suppresses hyperuricemia. Without going into details let me say that we concluded that hyperuricemia was inherited as a single autosomal factor with incomplete penetrance, more marked in the female than the male. Penetrance in men was estimated at 84% in the heterozygous male and 12% in the heterozygous female. The data did not allow gene frequency estimates because the incidence in the general population could not be computed. It is assumed that gout occurs only in individuals with idiopathic hyperuricemia. What proportion of them develop the disease is not known.

Wolfson[3] has recently advanced a new theory of gout. He believes that the inherited susceptibility to gout, an idiopathic hyperuricemia, depends upon an abnormal male sex-hormone from the adrenal which interferes with uric acid excretion by the kidney and thus produces hyperuricemia. These abnormal sex-hormones do not become effective until puberty and are counteracted by normal female ovarian effects present until the menopause. These abnormal male sex-hormones produce effects abnormally marked on uric-acid metabolism but normal on masculinity. Attacks of clinical gout depend upon a second endocrine disturbance—an inability to produce promptly and in adequate amounts needed 11-oxysteroids during periods of stress due to failure of the pituitary gland to release adequate amounts of ACTH. This explains the well-known clinical phenomena of gouty patients' susceptibility to attacks after any fracture, surgical procedure, hemorrhage or transfusion. We might include in this list any holiday meal like Christmas or Easter, any beer-drinking party, or other types of excess.

TREATMENT

The treatment of gout can be considered under two headings—the treatment of an acute gouty attack, and the treatment of chronic gout to prevent the accumulation of uric-acid or to encourage the solution and removal of uric-acid tophi. The successful management of acute gouty attacks can be accomplished with any one of 3 drugs.

(1) The oldest and best known is colchicine, the alkaloid of the meadow crocus. Colchicine is used in 1-mg. doses every 2–4 hours until relief is obtained or until diarrhea occurs. Unfortunately some patients can not tolerate colchicine in therapeutic doses. They think that the cure is worse than the disease and so the usefulness of the drug is limited.

(2) ACTH is effective in most gouty attacks, even in those refractory to colchicine, if given in adequate doses. Gutman recommends 50–200 mg. injected on the first day of treatment, with 50–100 mg. for the next day or two, after which the dose is tapered off. At this time colchicine is usually started, 1–2 mg. per day. If ACTH is stopped suddenly a recurrence is often seen.

(3) The most recent addition to our armamentarium

is phenylbutazone. This drug given in daily doses of 0·6-0·8 g. usually gives rapid relief. Gutman[4] noted complete remission in 24 hours in 13 of 20 acute attacks. Phenylbutazone is toxic, but for the short periods used in acute gout toxic symptoms rarely occur.

In patients subject to frequent attacks of gout the uninterrupted prophylactic administration of colchicine, 0·5-2·0 mg. daily, has been effective in many patients.

Gutman speaks of secondary gout. What he means is hyperuricemia secondary to some other disease such as polycythemia, leukemia, myeloid metaplasia, pernicious anemia and chronic hemolytic anemia. We found hyperuricemia also in cardiac failure, malignancy, pneumonia and hemorrhage, but have never seen the condition associated with acute gouty attacks or with tophus formation despite astronomical heights of hyperuricemia.

Great advances have been made in the treatment of chronic gout and the control of the formation of uric-acid tophi. When one considers how extensive and how severe tophus formation can be one realizes the importance of the problem. When one realizes that these very deforming and disabling complications occur very slowly over a long period of years and that the only method of treatment used to be surgical removal, the importance of recent satisfactory experience is emphasized. Dramatic examples are not uncommon.

The successful management of chronic gout depends upon the maintenance of the patient in a negative uric-acid balance. The rate of uric-acid accumulation is slow and varies from patient to patient and from time to time, tending to increase as age advances. Therapy is desirable whenever tophus formation is discovered. A negative uric-acid balance is accomplished by reducing uric-acid formation as far as possible and by increasing uric-acid elimination. Uric-acid excretion cannot be accurately estimated because some of it is destroyed by bacterial action in the stool. The reduction in uric-acid production can be judged by the fall in urinary excretion and it is evidenced by lowering of serum uric acid. To judge the effectiveness of uricosuric agents urinary uric-acid excretion is first established by a low-purine, low-fat, fixed-protein diet and then determining the increased uric-acid excretion. These measures usually cause a decrease in the blood level of uric-acid, favoring the flow of uric acid from the tissues to the blood. In one man critically studied by Gutman[5] the total mobilizable uric-acid amounted to 100 g. in 1 year in a patient with advanced tophaceous gout. The prolonged negative uric-acid balance becomes apparent because of the failure of new tophi to develop and because of the decrease in size or the disappearance of established tophi.

Dietary regulation cannot completely eliminate uric acid from the human metabolism. Uric-acid production continues during complete fasting. The quantity of uric-acid formed may be increased 100% by adequate amounts of purine substances and large amounts of ingested animal protein. A high-fat diet causes uric-acid retention by suppressing renal excretion. Gutman recommends a basal diet low in purines, poor in fat, with 60-70 g. of protein derived exclusively from cereals, grain products, eggs, cheese, milk, non-leguminous vegetables and fruits, with a total of 2,000 calories per day. After 2 weeks the uric-acid in the serum and the urine is determined. In the urine it has usually dropped by 200-300 mg. per day. Similar studies are made during the addition of 4 oz. of meat or fish daily. From these studies and the effects of probenecid administration the permissible quota of meat, fish or fowl is determined—usually 2-4 oz. several times a week or even daily.

Probenecid seems to be the uricosuric drug of choice. A single orally-administered dose of 2 g. a day usually increases uric-acid clearance fourfold and lasts nearly 24 hours. This is associated with a rapid decline in serum uric acid to a mean usually of half the pre-treatment level and within normal limits. This drug acts by suppression of renal tubular resorption and is highly selective. Side-reactions have been noted but they are usually mild and can be eliminated by reducing the dosage. Gutman reported, in the prolonged use of probenecid in 120 gouty patients, 19 instances of gastro-intestinal complaints, 15 of renal colic or passage of uric-acid gravel, 13 of exacerbations of gouty attacks, and 6 of drug allergy. Discontinuance was necessary in 14 cases. The reduction in size of tophi has been demonstrated in illustrations by Gutman.[5]

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THE MEDICAL DENTAL AND PHARMACY AMENDMENT BILL

SECOND READING DEBATE IN THE HOUSE OF ASSEMBLY

BY OUR PARLIAMENTARY CORRESPONDENT

The Medical, Dental and Pharmacy Amendment Bill was read a second time in the House of Assembly on 7 February 1957. It is substantially the same as the Bill which was before the House last session* but not brought to a conclusion. Although the Bill deals with several matters the question of blood transfusion proved to be the main subject of discussion.

* Report (1956): S. Afr. Med. J., **30** 549.

The Bill was introduced by the Minister of Health, *Mr. J. H. Viljoen*, who announced that the amendments provided for in the measure were largely at the request of the statutory bodies controlling the medical, dental and pharmaceutical professions.

Clause 1 of the Bill restricts to South African citizens by birth or descent, or domiciled in the Union when commencing professional studies, the right to register a medical qualification not prescribed under section 22 of the principal Act (but prescribed under Section 23).

It also provides for compulsory imprisonment without the option of a fine for a second offence of trafficking in any habit-forming drug, including dagga.

Mr. Viljoen referred to the employment of doctors by certain bodies. The conditions under which applications must be invited and under which applicants accepted service, had up to the present been controlled to a certain extent by the Medical Council. The Bill now legalized the rules of the Council regarding the acceptance of professional appointments by doctors and dentists.

Another amendment dealt with the payment of subsistence allowances to civil servants who were members of the S.A. Medical and Dental Council, when they had to serve on the council. There was also an amendment dealing with the home treatment of drug addicts in certain approved cases.

BLOOD TRANSFUSION SERVICES

Mr. Viljoen said the powers of the Minister for the promulgation of regulations for the control of blood transfusion services were extended under the Bill.

'This amendment has become necessary in view of the fact that the law advisers are of the opinion that the existing Section under the Act is not wide enough to cover the draft regulations which have been drawn up in collaboration with interested organizations,' he said. 'In this respect I can only refer to the three or more fatal cases which occurred in Cape Town last year. Public opinion throughout the entire country has practically insisted that certain regulations be drafted by the Minister so that a repetition can be avoided by exercising stronger and better control over the blood transfusion services. The amendment gives the necessary power to the Minister.'

Dr. H. Gluckman, M.P. for Yeoville and a former Minister of Health, said he wished to focus the attention of the Minister on the dangers which experts maintained existed in the divided responsibility in blood transfusion services.

'In some services you have the blood transfusion bottles sterilized by one authority or agency,' said Dr. Gluckman. 'Another authority carries out the blood testing, and yet a third administers the blood when a transfusion takes place. Experts maintain that the responsibility for the safety of blood transfusions from donor to patient is indivisible, and that the science of blood transfusion is one of serology and clinical practice—in other words, that whatever regulations are promulgated an effort should be made to avoid as far as possible some of the contributing factors responsible for the tragedies in Cape Town.'

Dr. Gluckman said the aim of the regulations, when they were promulgated, should be to guarantee the greatest standards of safety for both patient and donor, and not so much—as it was inclined to be in some cases—the standardization of blood transfusions throughout the country. He pointed out that there was a provision in the Bill which would enable the Minister, if he decided to do so, to draft regulations dealing with the racial identification of human blood intended for transfusion.

'Until now the only data which have been required by law, at any rate, to identify blood for human transfusion, were scientific, intended solely and primarily to ensure the greatest safety in the administration of blood. That is the first point I want to make. The second is that as far as I know there is no scientific evidence to support the view that there can be any conceivable danger, provided of course that the other factors which are applicable to transfusions anywhere are observed, in giving blood from one member of the human species to another.'

Dr. Gluckman said his third point—and this was debated and stated at the Durban conference where draft regulations dealing with this matter were considered—was that the transfusion services in South Africa, as far as practicable, did not transfuse blood from non-White donors to White recipients. That was done in deference to the known prejudices which most South Africans had in this matter.

'If that had been observed, then I fail to see where the need arose to make this a statutory enactment, why there was any need at all to focus attention on what was a traditional procedure and to drag it into the legislature.'

Dr. Carel de Wet, M.P. for Vereeniging District, was of the opinion that regulations should be promulgated to ensure that blood containers, once the blood had been used, were discarded. The time was past when bottles should be sterilized and the same containers used over and over again. The same applied to bleeding sets.

He also felt that when blood was sent to any place in South Africa, it should be accompanied by a complete record so that a doctor would know what type of blood it was, where it came from and whatever other information he needed. Furthermore, before a transfusion was made, the blood to be used should be compared once again with that of the patient in order to ensure compatibility.

Although many things were already being done by the medical profession on its own initiative, this did not relieve the Government of its responsibility, and for this reason it was necessary that provision be made in the Bill for the Government to promulgate regulations in regard to transfusion services.

'Honourable members have probably noticed that there has been a controversy in the Press about so-called blood apartheid', said Dr. de Wet. 'In the first place I want to express my deepest regret that the word "apartheid" has ever been mentioned in this regard. This whole controversy was untimely and misleading and could only have been calculated to evoke sensation.

'These articles which appeared in the Press, were not only incomplete, but they were passed off as scientific articles and scientific statements. They have done great harm to South Africa. In this regard certain members of the medical profession, particularly in Johannesburg, have been very guilty. Because of their actions there is a strong element of fear among many people that, should they require a blood transfusion, they would be given non-European blood.

'We as members of the medical profession cannot remain aloof from the emotions and sentiments of our patients. It is in any case always the duty of a doctor to eliminate, as far as possible, those elements which cause tension, because these elements in no way benefit the patient'.

RACIAL ORIGINS

After stating that South Africa had made a material contribution to the development of blood transfusion in the world, Dr. de Wet said that while there were undoubtedly differences in the blood of different races, these differences were not individual, so that generally speaking it was impossible to recognize the racial origin of a blood sample. For that reason the application of a blood transfusion was based not on its racial origin, but on whether it was compatible with the blood of the recipient, although it had been the practice on the part of blood transfusion services in South Africa and Rhodesia to differentiate between the blood given by White and non-White donors.

Dr. de Wet urged that, in view of the rapid development of blood transfusion, where the Minister was contemplating the appointment of a committee to advise him on blood transfusion services, this body should be a standing committee.

He also urged that it should be laid down by regulation that no European donor should be remunerated. He did not recommend that the same stipulation should apply to non-Europeans, because it was a tremendous problem to get non-European donors.

'Another matter I would like to mention is that the Minister should give his attention to the cost of blood transfusion. I find it alarming that blood is given free of charge by donors, but that in some cases it costs as much as £5 to £8 a pint to receive blood. This seems to me to be out of all proportion.

'The Minister should also give attention, in the regulations, to the labels on bottles containing blood. I feel that there should not only be a number on the bottle, but also the name, age and race of the donor.'

NEW PREPARATIONS AND APPLIANCES : NUWE PREPARATE EN TOESTELLE

'*Benzedrex*' *Inhaler* will shortly be put on the market to replace the well-known Benzedrine Inhaler. This announcement is made by M. and J. Pharmaceuticals (Pty.) Ltd., who supply the following statement:

'Benzedrex' Inhaler contains the volatile vasoconstrictor propylhexedrine. The inhaler has the same pleasant smell as the older Benzedrine Inhaler—but is more effective, giving faster, safer relief from nasal congestion.

Propylhexedrine produces virtually no central nervous stimulation, no matter how large the dose.

These advantages make 'Benzedrex' Inhaler an even better pocket treatment for the symtomatic relief of nasal congestion.

COST OF DIAGNOSIS

On 23 March 1956, a delegation of members of Federal Council's Subcommittee on Medical Fees for Private Practice (Dr. A. Landau, Chairman), together with Drs. J. H. Struthers and A. W. S. Sichel, was received by the Executive Committee of the South African Medical and Dental Council in Cape Town. The matter discussed was chiefly the working of section 80*bis* of the Medical, Dental and Pharmacy Act and the procedure adopted by the Medical Council in the assessment of doctors' accounts about which complaints are lodged under that section.

As a result of the discussion, and on consideration of particulars submitted in a letter written by the Registrar of the Medical Council on 28 May 1956, the Subcommittee reported to Federal Council in October 1956, that the points raised by the Subcommittee at the discussion on 23 March were satisfactorily answered. The Subcommittee added that no doctors had sent in complaints to the Association concerning the manner in which section 80*bis* had been applied.

The Registrar of the Medical Council wrote a further letter on 19 June 1956 on the subject of complaints regarding accounts for extensive examinations and investigations about the cost of which the patient had not been informed by the attending practitioner.* This letter was also before Federal Council at its meeting of October 1956, and on the instruction of Federal Council it is now published, as follows:

REGISTRAR'S LETTER

With further reference to the Conference between representatives of your Association and the Executive Committee of my Council which was held in Cape Town on 3 March 1956, I have now been directed by the Executive Committee to forward you the following views of the Executive Committee:

Since the meeting held in Cape Town on 23 March 1956 the Executive Committee desires to express the opinion that it would have been wise to draw the attention of your Committee and through it the attention of the profession as a whole, to a certain practice which not uncommonly leads to complaints under Section 80*bis*.

The attention of the Executive Committee has been drawn particularly to this fact by several complaints received during the last few months and feels that many of these complaints might have been avoided if practitioners had explained to their patients or their guardians what certain 'examinations or investigations' and/or treatments are likely to have cost. The type of case to which the Executive Committee refers may be illustrated by the following:

1. A practitioner informs a patient that he wishes him or her to enter a hospital or nursing home for a day to investigate the renal tract. The charge of the hospital may be discussed but nothing is said about further medical fees for treatment or for other doctors and the patient just thinks he is going in for a more thorough examination. At the end of the month the patient is very surprised to receive an account for 2 or 3 guineas for a consultation, 9 or 10 guineas for a pyelogram etc., 5 guineas or more for X-rays, 3 guineas or more for an anaesthetic fee and a fee from a pathologist for examination of the urine. The bill may come to 15-25 guineas and the patient refers it to the Medical Council with the comment that the account is 'fantastic'.

2. A patient is sent by a practitioner to a pathologist for a blood examination. Naturally the patient thinks this is an examination which will cost possibly 2 or 3 guineas, but the blood examination has been a very full one, including examination of 17-kestosteroids and corticosteroids (examinations which a doctor knows, or should know, is costly) and the patient is naturally surprised and indignant when he receives an account for about £19.

3. A patient is sent to a Nursing Home for psychiatric treatment and is informed that the Nursing Home charge will be so much per day, but is quite unaware that shock treatment will be administered 10, 20 or 30 times at a fee of 3 to 4½ guineas each time and the patient, or husband or guardian is dumbfounded at getting an account for 30 or even 135 guineas for this treatment alone.

These are no examples of individual cases but are given as the type of complaint with which the Executive Committee often has to deal and the Committee feels that with a proper explanation beforehand many of these complaints would never arise. It is only natural in such circumstances that a patient or guardian should feel that he should have been informed of what an 'investigation and/or treatment' was likely to cost and only natural that he should react somewhat vigorously when he receives a large account for something which he did not anticipate. Some complaints even question the right of a doctor to charge fees on behalf of another doctor whom they have never seen and for whose services they have not given consent. Others state that if they had known what the charges would be, they would not have consented to such investigations for they could not afford them and some other arrangements would have to have been made.

The Executive Committee is not stating that the fees are excessive—they may be quite fair fees for the services rendered—but it wishes to draw attention to the fact that the patient or guardian in such cases feels that he has been charged fees which appear to him excessive, simply because his attention has not been drawn to the nature of such investigations and what they are likely to cost. The Executive Committee is quite well aware that in some cases the facts given by the complainant may not have been correct and the doctor may have explained beforehand what the cost is likely to be, but there appears to be sufficient evidence to state that in many cases no explanation has been given beforehand.

The Executive Committee feels that it is only fair that the person responsible for the fees should be given some idea of the cost, before consenting to such investigation, and is of opinion that this would lead to fewer complaints, to better doctor-patient relationship and to fewer allegations of commercialism in Medicine.

* An editorial was published on this subject in the *Journal* of last week (**31**, 115).

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IN MEMORIAM

JAMES H. HUDSON, M.B., B.S. (DURH.)

Dr. James Hougham Hudson qualified at the University of Durham in 1927 and took over the practice of his father, the late Dr. C. H. Hudson. The latter, the son of a former magistrate of Graaff-Reinet, practised in that town all his professional life. His death on 29 December 1956 was totally unexpected. He seemed particularly well and fit and was engaged in active practice. Without any premonitory signs he sustained a massive coronary occlusion and passed away within an hour of the first onset of pain.

Dr. J. H. Hudson

Dr. J. van Schalkwyk, of Graaff-Reinet, writes: Dr. James Hudson was a skilful and conscientious practitioner in all the branches of medicine. Of a quiet, gentle, retiring disposition he was always a gentleman—greatly beloved by his patients and respected and liked by his colleagues. His only interest in public life was the Graaff-Reinet Gem Theatres, of which he was Chairman.

He leaves a widow, who was a former nurse at the local Hospital and daughter of a colleague, and two sons. One is farming in Rhodesia, and the younger one is still at University. His early and untimely death at the age of 52 came as a shock, and is a great loss to the community, to his friends and to his colleagues. Inscrutable are the ways of Providence.

PASSING EVENTS : IN DIE VERBYGAAN

Workmen's Compensation Act. Medical practitioners are asked to communicate with Dr. M. J. Bailey, Hon. Secretary of the Cape Western Branch of the Association, Medical House, 35 Wale Street, Cape Town (P.O. Box 643, Telephone 3-1574) before applying for the positions advertised by the City of Cape Town on page xxv of last week's issue of the *Journal* (9 February 1957). The advertisement in question refers to the appointment of a panel of 15 part-time medical officers to attend municipal employees injured on duty and retain such fees as are paid by the Workmen's Compensation Commissioner.

Wet op Skadeloosstelling vir Werknemers. Mediese praktisyns word versoek om met dr. M. J. Bailey, ere-sekretaris van die Tak Wes-Kaapland van die Vereniging, Mediese Huis, Waalstraat 35, Kaapstad (Posbus 643, Telefoon 3-1574) in verbinding te tree alvorens hulle aansoek doen om die betrekkings soos geadverteer deur die Stad Kaapstad op bladsy xxv van verlede week se uitgawe van die *Tydskrif* (9 Februarie 1957). Die betrokke advertensie verwys na die aanstelling van 'n groep van 15 deeltydse mediese beamptes om munisipale werknemers, wat op diens beseer is, te behandel, en dat sodanige gelde soos deur die Kommissaris van Skadeloosstelling vir Werknemers betaal word, behou kan word.

* * *

Dr. David Ordman, Head of the Allergy Department of the South African Institute for Medical Research, Johannesburg, has been elected a Founder Member of the International Association of Asthmology. He has also been appointed to the Committee for the Bioclimatic Study of Allergic Diseases of the International Society of Bioclimatology and Biometeorology.

* * *

Second World Conference on Medical Education. Dr. Raymond B. Allen, Chancellor, University of California, Los Angeles, has been named President of this Conference, which is to be held in Chicago, USA, from 30 August to 4 September 1959 (see *Journal* of 20 October 1956—**30,** 1021). At the First World Conference

on Medical Education, which was held in the United Kingdom, the late Sir Lionel Whitby was President.

* * *

Union Department of Health Bulletin. Report for the 7 days ended 24 January 1957.

Plague, Smallpox, Typhus Fever: Nil.

Epidemic Diseases in Other Countries.

Plague: Nil.

Cholera in Chalna, Dacca (Pakistan).

Smallpox in Ahmedabad, Allahabad, Bombay, Calcutta, Cuddalore, Kanpur, Quilon, Tiruchirappalli (India); Makassar, Tjirebon (Indonesia); Baghdad, Mosul (Iraq); Kuwait; Chalna, Dacca, Karachi (Pakistan).

Typhus Fever: Nil.

Union Department of Health Bulletin. Report for the 7 days ended 31 January 1957.

Plague, Smallpox, Typhus Fever: Nil.

Epidemic Diseases in Other Countries:

Plague: Nil.

Cholera in Calcutta (India); Chalna, Chittagong, Dacca (Pakistan).

Smallpox in Rangoon (Burma); Ahmedabad, Allahbad, Bombay, Calcutta, Cuddalore, Delhi, Kanpur, Madras, Quilon, Tiruchirappalli, Visakhapatnam (India); Makassar, Tjirebon (Indonesia); Baghdad, Mosul (Iraq); Kuwait, Dacca, Karachi (Pakistan); Nairobi (Kenya).

Typhus Fever in Cairo (Egypt).

REVIEWS OF BOOKS : BOEKRESENSIES

NEUROSES IN GENERAL PRACTICE

Neuroses in General Practice. Being the Second John Matheson Shaw Lecture of the Royal College of Physicians of Edinburgh—Delivered in the Hall of the College on 11 November 1955, by C. A. H. Watts, M.D. Pp. 31. 3s. 6d. Edinburgh: The Royal College of Physicians. 1956.

It is seldom that a reviewer can with true feeling give full marks to the book or pamphlet which he is reviewing; so often one feels that the Star has been used as a sycophantic short-cut through some dreary tome rather than as a mark of merit, but to Dr. Watts' lecture on Neuroses in General Practice, which was delivered a little over a year ago in Edinburgh, one has no hesitation in giving a full award for excellence and worth. Not only does this paper correct the impression that psychotherapy is beyond the bounds of general practice and 'functional' cases are dull and time-consuming, but it emphasizes the defects in our system of medicine which allows the neurotic to be treated with indifference and deplores the attitude which regards psychoneurotic maladies as matters for disciplinary action rather than for sympathy and understanding.

Dr. Watts has written a great deal on the problem of various forms of neurosis met with in general practice and some of his aphorisms are well worth remembering. 'When the patient blames his organs for his symptoms he is usually neurotic: when he blames his "nerves" he is usually depressed', is an adage which we might all keep in mind.

This booklet is one which carries a message of understanding to all those who have to deal with the neurotic in contrast to the psychosomatic patient, and if every medical student in his final year were to read it and digest it he would turn to general practice with the respect it deserves and not regard it, as it is in danger of being regarded, as a sieve which filters off cases to the various specialists.

J.MacW.MacG.

VARIOUS TROPHIC CONDITIONS OF THE LOWER LIMBS

Les Troubles Trophiques Des Membres Inférieurs D'Origine Veineuse. Published under the direction of Jacques Charpy and Marius Audier. Pp. 376. 156 Figures. 2.500 fr. Paris: Masson et Cie. 1956.

Contents: I. *Introduction* by M. M. Audier (Marseille). II. *Six Reports*, by MM. H. Jausion, A. Roussel, R. Veiville, R. Sylvestre and J. Chevrier; M. J.-D. Martinet (Paris); MM. M. Mairano (Turin), R. Castagna and G. Impallomeni; MM. M. Pierre (Marseille) and A. Gaté (Lyon); M. F. Martorell (Barcelone); and MM. G. Tramier, C. Bourde, E. Bourdoncle, P. Y. Castelain (Marseille). III. *Communications:* 5 General, by MM. Cl. Huriez, F. Desmons and P.-H. Pelce (Lille); MM. A.-G. and E. Calas (Marseille). 6 Etiological, by MM. J. van der Stricht and M. Simons (Bruxelles); MM. A. Boncinelli et C. Sabatini (Modène); M. E. Krieg (Fribourg-en-Brisgau); M. A. Mathieu (Marseille); M. J. Vague (Marseille); and M. P. Walois (Paris). 2 Clinical, by M. S. Noguermore (Barcelone); and MM. A.-G. Calas and E. Calas (Marseille). 9 Biological, by M. A. Castellani (Lisbonne); M. A. Delmotte (Bruxelles); M. M. Comel (Pise); M. E. Mian (Pise); MM. E. Biagini and G. de Angelis (Pise); M. Gl. Bassi (Pise); MM. V. Cordonnier and P. De-beer (Lille); M. P. Temine (Marseille). 3 Radiological and Capillaroscopic by M. O. Gilje (Oslo); MM. O. Gilje and I. Andersen (Oslo); and M. W. Richter (Bonn). 18 Therapeutic by MM. P. Rimbaud, Étienne and Lisbonne (Montpellier); M. H. Chatard (Grenoble); MM. J. Sourdille and P. Vigier (Nantes); M. A. Gélin (Bruxelles); MM. Y.-J. Longuet and O. Lièvain (Paris); M. G. Arnulf (Lyon); MM. R. Tournay (Paris) and J. Marmasse (Orleans); M. H. Saglio (Paris); M. J. Marmasse (Orléans); M. R. Tournay (Paris); M. J. Babilliot (Paris); Mme. E. Loewy (Tunis); M. H. Saglio (Paris); M. I. Kohen (Paris); M. A.-G. Muller (Paris); MM. R. Nadal and G. Gérard (Paris); M. A. Fière (Marseille); and M. F. Beurier (Aix-en-Provence). General Discussion.

This is a collection of papers delivered at the Colloquium held at Aix-en-Provence in October 1955, on the trophic disturbances of venous origin in the lower extremities arranged by the French Society of Dermatology and the International Society of Phlebology.

It is impossible to review the papers in detail; there are some 50 in all, dealing with all aspects of the problem both academic and practical.

A great deal of space is taken up by excellent pathological and anatomical studies of crural ulcers, in which the French school has always been particularly interested and under the leadership of such notable scientists as Gougerot, Laubry and le Riche has developed an approach and terminology of its own.

This stimulating volume should be read by all working in this field, for it affords a convenient way of acquainting oneself with the current views and ideas of the French school.

R.H.G.

PSYCHOLOGY

Essentials of Psychology. Second Revised and Enlarged Edition of *What is Psychology.* By Werner Wolff. Pp. xiv + 385. 92 Figures. 86.50. New York and London: Grune & Stratton, Inc, 1956.

Contents: Preface. *Part I: The Scope of Psychology.* 1. Origins of Psychology. 2. Definitions and Fields of Psychology. 3. Three Major Psychological Viewpoints. 4. Methods of Psychological Research. 5. Psychology and the Other Sciences. 6. Is Psychology a Science? *Part II: The Physiology of Behavior.* 7. The Origin of the Individual. 8. The Brain and the Nervous System. 9. The Electro-chemical Basis of Psychological Activity. 10. The Senses. *Part III: Perception.* 11. Sensation and Perception. 12. Laws of Perception. 13. Dynamics of Perception. 14. Need and Perception. 15. Perception and Society. *Part IV. Retention.* 16. Memory and Its Measurement. 17. The Organizing Functions of Memory. 20 Symbolization and Memory. 19. The Learning Process. 20. Learning Theories. 21. The Directive Idea. *Part V: Thinking.* 22. Origins of Thinking. 23. Thought and Association. 24. The Organization and Mechanism of Thought. 25. Theories of Thinking. 26. Types of Thinking. 27. Thinking and Education. *Part VI: Intelligence.* 28. The Influence of Heredity and Environment. 29. Intelligence and Aptitude Tests. *Part VII: Emotion.* 30. The Structure of Emotion. 31. Theories of Emotion. 32. The Physiology of Emotion. 33. Reactions to Interference. 34. Integrative Responses. 35. Emotion and Expression. *Part VIII: Personality.* 36. Definitions of Personality. 37. Physiology and Personality. 38. Psycho-somatic Theories of Personality. 39. Psychological Theories of Personality. 40. Diagnosis of Personality. *Part IX: Attitudes.* 41. The Concept of Attitude 42. Attitudes and Environment. 43. Attitudes and Culture. *Part X: Motivation.* 44. The Structure of Motivation. 45. Sigmund Freud. 46. Alfred Adler. 47. Carl Gustav Jung. 48. Psychology of Interpretation. 49. The Application of Psychology. Bibliography. Author Index. Subject Index.

Professor Wolff states in his introduction, 'The present survey aims not at mere classification of data but at their interrelationship, not at the surface but at the depth of behaviour'. But if we may be excused the use of a cricketing idiom for this transatlantic thrower we might say that it is not enough for the bowler to know he should hit the wicket, he must occasionally do so. The

author of this book, despite many well-chosen excerpts from Plato, Aristotle, Nietzsche, Rimbaud, Thomas Mann and others, has given us a series of disconnected snippets without any view of the whole man. Indeed we are left with the impression that the psyche is something which can be caught in a series of neat tests, altered by a number of glandular extracts, and measured by graphs. Much of what is written is fresh, succinctly put, and memorable, but one never finds any coordinating direction nor enveloping light. It is rather as if of two methods of lighting a room, either by a strong hidden illumination or by a series of scattered punctate bulbs, Professor Wolff has chosen the latter method. William James chose the former, and although his book, of much the same length as this present one, was written in 1890 and has nothing about conditioned reflexes, Gestalt, or the super-ego it is incomparably the better simply because it attempts to look at Man from within and not from the external viewpoint of the experimental psychologist.

To end with a quotation from James that Wolff himself uses, one feels that this volume is, like the world to the infant, 'one big blooming buzzing confusion', but its illustrations are fascinating, amusing and not uninstructive.

J.MacW.MacG.

CARDIOVASCULAR SYSTEM IN VIRUS DISEASES

Virus Diseases and the Cardiovascular System. By Ernest Lyon, M.D. Pp. viii + 215. 85.75. New York and London: Grune & Stratton, Inc. 1956.

Contents: Preface. Foreword—Paul D. White, M.D. *Part One.* I. General Remarks on Viruses, Viral Infections and Associated Cardiovascular Involvement. II. Present Cardiovascular Concepts of Virus Diseases: The Capillary Syndrome in Viral Hepatitis, The Capillary Syndrome in Poliomyelitis, The Capillary Syndrome in Smallpox, The Capillary Syndrome in Epidemic Hemorrhagic Fever. *Part Two.* III. Exanthematous Diseases: Measles, German Measles, Variola, Varicella, Herpes Zoster, Herpes Simplex. IV. Diseases of the Eye: Newcastle Disease, Behcet's Disease. V. Respiratory Diseases: Influenza, Virus Pneumonia, Interstitial Pneumonia in Infants, Psittacosis, Ornithosis, Lymphopathia Venereum, Cat Scratch Disease, Mumps, Cytomegalic Inclusion Disease. VI. Liver Diseases: Hepatitis A and B. VII. Neurotropic Virus Disease: Viral Encephalitides and Encephalomyocarditis, Poliomyelitis, Rabies. VIII. Diseases of the Muscular System: Coxsackie Virus Diseases—Herpangina, Epidemic Pleurodynia. IX. Fevers of Viral Origin Spread by Arthropods: Yellow Fever, Dengue Fever, Sandfly Fever. X. Diseases of Uncertain but Possibly Viral Etiology: Hamman-Rich Syndrome, Infectious Mononucleosis, Epidemic Hemorrhagic Fever. *Part Three.* XI. Pathology and Clinical Features of Rickettsial Infections, with Special Reference to the Cardiovascular System: Pathology of Rickettsial Diseases, Clinical Features of Rickettsial Diseases, Therapeutics, Special Histopathological and Clinical Features. Addendum. Index.

This book by Ernest Lyon with a Foreword by Paul D. White, was approached by the reviewer with considerable anticipation. At some time or another most of us have encountered virus diseases with unexplained disproportionate tachycardias, ectopic rhythms and even cardiac failure. There have been numerous isolated reports referring to involvement by viruses of the blood vessels, the myocardium and even the pericardium.

Dr. Lyons reviews many of these reports and attempts to weigh the evidence for and against such an entity. The observations are clinical, electrocardiographic and pathological. The author feels that there is good evidence for capillary damage with increased permeability. While generally he tends to cast his vote with the ayes, the case remains unproven as the pathological changes are not specific and may be produced indirectly. Thus, while heart involvement has been reported in influenza, yellow fever, smallpox, encephalitis, poliomyelitis, mumps, measles and glandular fever, and in other diseases, and the pathological changes are said to include cellular infiltration, oedema, focal necrosis and haemorrhages, there are still differences of opinion about the casual relationship.

The book deals with both virus and rickettsial diseases, which are presented individually in the conventional manner, including description, clinical picture etc. Part one is undoubtedly the best. Each chapter is followed by a number of references.

Those wishing for a clear, concise account of virus and rickettsial diseases will find this a useful little volume. One feels that, while reference is being frequently made to the relation between viruses and the cardiovascular system, it remains more a concise account of virus diseases.

I.G.

DERMATOLOGY

An Introduction to Dermatology. Twelfth Edition. By G. H. Percival, M.D., Ph.D., F.R.C.P., D.P.H. Pp. vii + 374. 256 Illustrations, 188 in full colour. 45s. net + 1s. 1d. postage abroad. Edinburgh and London: E. & S. Livingstone Ltd. 1956.

Contents: I. Anatomy, Physiology and Pathology of the Skin. II. Classification, Diagnosis and Prognosis. III. Treatment. IV. Erythematous Eruptions. V. The Urticarias and Purpura. VI. The Herpetiform and Idiopathic Bullous Eruptions. VII. Eczema. VIII. Eczema and Dermatitis. IX. Avitaminosis. X. Psoriasis, Pityriasis Rosea, Lichen Planus, Pityriasis Rubra Pilaris, Generalised Exfoliative Dermatitis. XI. Superficial Bacterial Infections and Vaccinia. XII. Diseases due to Animal Parasites. XIII. Diseases due to Vegetable Parasites. XIV. Diseases due to Vegetable Parasites. XV. Infective Granulomata. XVI. Tropical Skin Diseases. XVII. The Reticuloses. XVIII. Disorders of the Skin Appendages. XIX. Disorders of the Skin Appendages. XX. Disorders of the Skin Appendages. XXI. Dystrophic Cutaneous Disorders. XXII. Anomalies of Sensation. XXIII. Benign Cutaneous Tumours. XXIV. Malignant Cutaneous Tumours. Index.

The appearance of a 12th edition of this compact and well illustrated little book proves its continued popularity with British medical students. Fresh material has been added on the modern antibiotics, cortisone etc. and on the classification of the bullous diseases.

In a book of this size drastic compression of some subjects is unavoidable but there are limits to any author's powers of succinct expression. The note on purpura (1½ pages, including a large photograph) does not begin to explain the phenomenon.

Some of the author's concepts will not be acceptable to all dermatologists. Cheiropompholyx is still described as a disease entity which 'seems to be due to altered activity of the sweat glands due to nervous or toxic causes'. The section on sarcoid (*sic*) is confusing and seems to imply that sarcoid is a tuberculid while sarcoidosis may be a disease of the reticulo-endothelial system. Erythema induratum is classified as a variety of sarcoid. Urticaria pigmentosa is still classified as a form of urticaria and no mention is made of the role played by insects in urticaria papulosa.

The old terminology is used in the classification of leprosy and it is stated that 'the nodular variety almost invariably passes into the anaesthetic if the patient lives long enough'—a statement that is either ill-worded or incorrect.

Some revision seems indicated if this book is to perpetuate its long history as one of the better short texts on dermatology.

J.M.

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PAMPERING THE PUBLIC

To the Editor: If the doctor who wrote about discipline being applied to the general public (this *Journal* 26 January) believes that by that way he will lead a more carefree life, I suggest he change his job without delay. By trying to get people to worry him less for trivial complaints and imagined maladies he may stave off the early 'coronary' for himself but he will die of starvation before he is very much older.

The public *will* be pampered. It is not sufficient to practice good medicine today, in this country at any rate, and especially in the smaller towns. One has to be well versed in the art of 'boot-licking', and the more acrobatic one is in the performance of this feat the larger one's practice becomes. The young doctor will find that the more enthusiastic he is about rising at 2 a.m. for somebody's headache or insomania, when he knows that an aspirin or a glass of hot milk will suffice, the more he will be upheld as a paragon at the afternoon tea parties.

Disillusioned

30 January 1957